# HUMAN METABOLISM WITH ENEMATA OF ALCOHOL, DEXTROSE, AND LEVULOSE

BY

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# PREFACE.

The researches which are given in this monograph were carried out during the years 1915 to 1917, and in their conduct I was greatly assisted by a number of individuals. I wish to express my appreciation of the cooperation and the willingness of the four medical students who underwent this unusual form of study of metabolism. The determinations of the alcohol in urine and wash-outs were all made by Miss E. B. Babcock, whose mastery of the Nicloux method rendered it possible to supplement the studies of the respiratory exchange. The analyses of expired air and of the excreta were carried out for the most part by Mr. F. J. Murray and Mr. I. B. Simon, and they also assisted in the measurements of the respiratory exchange. It is a pleasure to acknowledge the great improvement in the manuscript as the result of the very careful editorial revision by Miss A. N. Darling.[1]

Nutrition Laboratory of the
Carnegie Institution of Washington,
*Boston, Massachusetts, December 15, 1924.*

[1] Died Jan. 25, 1925.

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THORNE M. CARPENTER

With ninety-one text-figures.

# HUMAN METABOLISM WITH ENEMATA OF ALCOHOL, DEXTROSE, AND LEVULOSE.

By Thorne M. Carpenter.

## INTRODUCTION.

The ingestion of food, drink, and medicine is usually by way of the mouth. The material then passes through the alimentary tract where it is prepared, if necessary, for absorption into the blood-stream, or else carried entirely through the alimentary canal and rejected unchanged. Under certain conditions, the taking of material by mouth is not feasible and, indeed, is well nigh impossible. Such conditions are coma, unconsciousness, inability or unwillingness of the individual to cooperate (as in insanity), congenital or accidental obstruction of the alimentary canal, and during or after anesthesia. The material must then be introduced in some other manner, the various paths used being intravenous, intramuscular, intraperitoneal, and rectal injection.

Rectal injections of saline and glucose solutions in operative procedures are common, but these are in most cases empirical. Attempts have been made to introduce rectally many substances, but there is a great deal of confusion of ideas and, in much of the experimental work, lack of uniformity in results, as to the metabolic utility of rectal injection. Undoubtedly much of the earlier work on rectal feeding, particularly with reference to protein, is of little value, because of the lack of knowledge as to how or in what form the food material was absorbed. There is thus need for a thorough, scientific study of the metabolism when nutrient material is injected by rectum. The results of such study should be of immediate value to clinicians and nutrition experts who are obliged to resort to this method.

Aside from its practical application, there is another way in which such a study is of value. Rectal introduction is an unusual and abnormal method of making nutritive material available. It is conceivable that the path or paths in the animal body through which the substance is carried may be different from those when it is ingested by mouth; consequently the steps in the cleavage of the material may be different in speed and character from those when food is taken by mouth. The method of studying the metabolism by the introduction of substances in various ways may be considered as a differential, topographic, or regional method, which conceivably would give results of value in the interpretation of physiological and biochemical processes.

In 1913, the Nutrition Laboratory published a program,[1] tentatively proposed, for an investigation of the physiological action of ethyl alcohol

[1] Benedict and Dodge: Tentative plan for a proposed investigation into the physiological action of ethyl alcohol in man. Proposed correlative study of the psychological effects of alcohol on man. Privately printed, Boston, Massachusetts, 1913. See, also, Dodge and Benedict, Carnegie Inst. Wash. Pub. No. 232, 1915, pp. 266–275.

in man. One of the methods of ingestion suggested in the program was that of rectal enema, either of alcohol alone or with glucose solutions. The experimental results reported in the present monograph are the outcome of a study of the physiological effect of alcohol when introduced in this manner.

It was originally intended in this research to investigate only the effect of alcohol upon the respiratory exchange, with particular reference to the absorption of the alcohol and to the change in respiratory quotient as an indication of the actual utilization of alcohol in the metabolism. The study subsequently led to the determination of the amount, composition, and alcohol-content of the urine. During the course of the experiments, observations were also made upon the effect of the injection of dextrose and levulose solutions.

The research began in 1915 and was carried out with four medical students. In the spring of 1917, two of these students entered military service and the other two were likewise no longer available, so that it was not feasible to continue the study with these men. Preliminary reports[1] of several phases of the investigation have been made, and a brief summary of results of a special group of experiments with rectal injection of a solution containing 7.5 per cent of alcohol by weight was given by Miles[2] in a recent monograph.

## PREVIOUS RESEARCHES ON RECTAL ALIMENTATION.

The rectal introduction of food and medicaments is very old historically. Bensaude and Vicente[3] review the history of the use of bile in medicine, stating that Egyptian papyrus thirteen centuries before Christ gave prescriptions for enemas. The writings of Hippocrates,[5,6,8] Galen,[4,5,6,8] and Celsus[4,5,6,7,8] mention the possibilities of nutrition by way of the rectum. The consensus of opinion in the literature is that modern scientific investigation of the utility of rectal injection began with the investigation of Voit and Bauer in 1869.[9] Their work, however, was not concerned with the materials used in the research reported here and is of historical interest only.

In the following section a review is given of the most important investigations upon rectal feeding with man and animals, with special reference to the introduction of alcohol, dextrose, and levulose. This review of the literature includes not only those researches in which studies were made of absorption or of respiratory exchange, but also such other researches as may assist in the interpretation of the results obtained from the series presented in this report.

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[1] Carpenter and Babcock: Journ. Biol. Chem., 1917, 29, Proc. Am. Soc. Biol. Chem., p. xxviii; Carpenter, Am. Journ. Physiol., 1917, 42, p. 605; *Ibid.*, 1922, 59, p. 440.

[2] Miles: Carnegie Inst. Wash. Pub. No. 333, 1924, p. 111.

[3] Bensaude and Vicente: Bull. et mém. Soc. méd. d. hôpitaux de Paris, 1919, 43, p. 932.

[4] Schoenborn: Zur Frage der Resorption von Kohlehydraten im menschlichen Rectum. Diss., Würzburg, 1897.

[5] Bial: Ausnutzung von Pepton- und Pepton-Alkohol-Klysmen. Diss., Halle, 1903.

[6] Zehmisch: Ausnutzung von Nährklystieren. Diss., Halle, 1903.

[7] Wendt: Ueber Anwendung, Indicationen und Erfolge der Ernährung per Rectum. Diss., Jena, 1896.

[8] Plantenga: Der Werth der Nährklystiere. Diss., Freiburg, 1898.

[9] Voit and Bauer: Zeitschr. f. Biol., 1869, 5, p. 536.

## RESEARCHES WITH RECTAL INTRODUCTION OF DEXTROSE.

The studies on the rectal introduction of dextrose, which are much more numerous than those with the other two materials, are first considered in chronological sequence.

*Eichorst, 1871.*—An extensive investigation upon the absorption of various food materials in the large intestine was carried out by Eichorst[1] with a dog as subject. In studying the absorption of milk sugar, Eichorst found an elimination of sugar in the urine. These results led to further studies on the absorption of sugar in which he employed honey. This was diluted and given to the dog by injection; the dog was fed a mixed diet at the same time. As the experimenter did not find so much sugar in the urine as he expected, he analyzed the feces and obtained sugar. The experiment continued 6 days. On the first day he gave 1 gram of honey and found in the urine 0.3 gram sugar and in the feces 0.6 gram. The amount given was gradually increased each day until, on the sixth day, the dog was receiving 16 grams. On that day he found 3.4 grams of sugar in the urine and 3.3 grams in the feces.

*Schoenborn, 1897.*—One of the most extensive researches on the absorption of dextrose was carried out by Schoenborn.[2] His investigations consisted of 10 experiments with 10 patients, with the quantity of sugar injected ranging from 25.0 grams to 174 grams; the time of retention varied from 1 hour to 29 hours. With 25 grams, the amount unabsorbed was from 3.5 grams to 15 grams; with 34 grams, the maximum amount unabsorbed was 9.2 grams.

At first he injected the solutions without using a previous cleansing enema, but later he gave an enema of 500 c. c. of water before the injection and the same amount for the final enema or wash-out. The quantity obtained from the final wash-out varied. To insure the entire removal of the sugar from the intestines by the wash-out, he occasionally used additional enemas, but reports that sugar was never found in the material obtained from the second. When the sugar was given in the ordinary way, i. e., by mouth, it was in no instance eliminated in the urine. With the largest quantity (174 grams), only 30 grams were found to be unabsorbed, leaving 144 grams as the actual absorption in 1 hour. Schoenborn believes that 1 to 2 hours is sufficiently long for the retention of the injection, as the maximum absorption occurred in the first hour.

Experiments were made in which special precautions were taken to prevent the sugar solution from passing into the portal system. For this purpose he introduced a dilatable bag into the upper part of the rectum. He found its introduction very difficult, but was successful in the third attempt. The balloon was introduced by means of a pair of tongs to about 10 cm. above the rectal opening. He then injected into the lower part of the rectum 150 c. c. of a 12 per cent sugar solution (about 18 grams of sugar). After the retention of the solution for 1 hour, the intestine was washed out and the urine sampled every 2 hours. The cleansing enema was given at 11 o'clock, but the resulting fluid was sugar-free, as was also the urine at 12 and 2 o'clock. At 4 o'clock there was sufficient sugar to determine (0.35 gram), and in the urine at 6 and 8 o'clock, there was still a reducing substance. The night urine was again sugar-free. He concluded that the sugar was absorbed through the middle hemorrhoidal vein. Thus it had

[1] Eichorst: Arch. f. d. ges. Physiol., 1871, 4, p. 570.

[2] Schoenborn: Zur Frage der Resorption von Kohlehydraten im menschlichen Rectum. Diss., Würzburg, 1897.

avoided glycogen formation in the liver, and a part was eliminated through the urine.

Schoenborn also had an opportunity to carry out additional experiments with a patient in the hospital, from whom 10 cm. of the lower end of the rectum had been removed. With this subject the balloon was inserted to a point 10 cm. higher than the new opening. A quantity of sugar solution with a low concentration was injected in the portion of the rectum below the balloon. The solution was retained for 1 hour and the urine sampled every 2 hours. No glycosuria appeared. The author's long series of results varied as to the absorption of the sugar introduced into the rectum, but on the whole they indicate a large absorption of glucose solution.

*Strauss, 1897.*—Strauss[1] was particularly interested in glycosuria after the injection of dextrose and milk sugar by rectum. He made experiments on 4 patients with whom the ingestion of 100 grams of dextrose by mouth showed a good tolerance. From 20 to 50 grams in a 10 per cent solution were given the patient in the morning. A number of experiments were also carried out in which larger amounts were given rectally in 20 per cent solutions, the largest being 100 grams in 500 c. c. of water. In some cases the enemas were retained only 1 or 2 hours; in other cases they were rejected after 2 or 3 hours. The urines were collected for several periods of 1½ hours each. In no case was sugar found in the urine. In another series of experiments, the sugar was given in the evening and the urine collected for two 2-hour periods, and then for the remainder of the night. In these observations, also, no sugar was eliminated in the urine. To 4 patients with whom 100 grams of dextrose taken orally produced glycosuria, he gave 100 grams of dextrose in 500 c. c. of water by rectum, the material being retained 45 minutes to 1 hour; no sugar was found in the urine. No details are given as to the amount actually absorbed in these experiments.

*von Leube, 1897.*—In a general discussion of the value of rectal feeding and the materials to be used, von Leube[2] reports two experiments. In one, 70 grams of dextrose were given in 300 c. c. of water and retained for 5½ hours in the rectum. The spontaneous stools were analyzed and it was found that 63.8 grams of the dextrose were absorbed. In the other experiment, 50 grams were given in 300 c. c. of water and retained for 12 hours, with an absorption of 46 grams. von Leube recommends a volume of not over 300 c. c. and concentrations of 10 to 20 per cent. He discusses the possibility of absorption by the lower and middle hemorrhoidal veins only, which would lead to glycosuria, but says that this never has occurred, so he believes that the injection goes into the colon and large intestine in such a way that the blood of the superior hemorrhoidal vein carries it to the portal circulation. He admits the possibility of fermentation, but believes that the difficulty is more theoretical than practical, as the major portion of the absorption takes place in the first hour, and this is too short a time for the entire amount to disappear by way of putrefaction.

*Müller, 1897.*—The purpose of a study made by J. Müller[3] was to determine whether acetone was formed in the digestive tract or in some other portion of the body. By use of a meat-fat diet, the subjects were brought to a condition in which acetone was eliminated in the urine and breath. After several days he tried intravenous injection of dextrose, but as tests on himself did not give good reactions, he decided to discontinue the use of this method of injection. He then resorted to rectal injection, giving 88 to 110 grams in volumes from 600 to 700 c. c. At first he allowed the enema to remain 5 to 7

[1] Strauss: Charité-Annalen, 1897, 22, p. 264.
[2] von Leube: Leyden's Handbuch der Ernährungstherapie u. Diätetik. Leipsic, 1897, 1, p. 496.
[3] Müller: Verhandl. d. Kongr. f. inn. Med., 1898, p. 454.

hours, but later only 2 hours, as he believed this was sufficient time for good absorption (about 50 per cent). He never found sugar in the urine. After 2 days of rectal injection of carbohydrate, he gave carbohydrate by mouth on 2 days in the form of rye bread.

There were three series of experiments. In the first, the average elimination of acetone in 4 days on a meat-fat diet was 197 mg. per 24 hours. He then injected rectally 56 grams and 50 grams of dextrose on 2 days. The average elimination of acetone for the 2 days was 387 mg. On each of the next 2 days, 50 grams of carbohydrate by mouth were given, with an average elimination of 127 mg.

In the second series the carbohydrate-free diet was taken for 11 days, with a mean average for the acetone eliminated by mouth and in the urine of 472 mg.; 3 days followed on which 43, 60, and 65 grams of dextrose were given by rectum, with a subsequent three days on which 40, 40, and 50 grams of carbohydrate were given by mouth. The average elimination of acetone with rectal injection was 468 mg. and with oral ingestion 212 mg. In the third series, on 5 days of a carbohydrate-free diet, the average elimination of acetone was 333 mg. With 3 days of dextrose injection (68, 62, and 58 grams), the average acetone elimination was 434 mg., and with 2 days of oral ingestion (45 and 30 grams), the elimination was 267 mg.

Müller concludes that carbohydrate prevents the formation of acetone only when it passes through the gastro-intestinal canal in a normal manner, that is, if carbohydrate enters the body by another way it is without influence. Then he draws the remarkable conclusion that the source of acetone formation must be in the intestinal canal.

*Schuman-Leclerq, 1901.*—In an extensive study on the influence of food upon the acetone excretion with himself as subject, Schuman-Leclerq[1] used dextrose and levulose by rectum. For 13 days he had a mixed diet and then for 25 days he took by mouth from 500 to 1,966 grams of meat, usually 1,000 grams. On a number of these meat days sugar was added to the diet, being taken by mouth or by rectum. The urine was collected in 24-hour periods and the acetone determined. There were 5 days with 25 to 50 grams of dextrose by mouth, 2 days with 50 and 100 grams of dextrose by rectum, followed by 4 days of meat diet only, and again with 50 grams of dextrose by rectum; another day with 25 grams of dextrose by rectum, and later 3 days with 50, 75, and 100 grams of levulose by rectum.

The data do not indicate positively in all cases that the carbohydrate taken by rectum lowered the acetone excretion, but there is a tendency toward lower values on the days on which carbohydrate was taken or on the day following; the nitrogen excretion in the urine was materially lower on many of the days on which the carbohydrate was taken rectally.

Bergmark[2] has criticized these experiments, saying that the acetone elimination was so variable that no conclusions can be drawn regarding the effect of rectal feeding of carbohydrate upon the acetone excretion.

*Reach, 1902.*—Reach[3] studied the respiratory exchange after oral ingestion of several sugars, including dextrose, and compared it with the respiratory exchange when the same material was injected by rectum. The experiments were carried out on a 27-year old man who was a patient in the hospital. His height was 152 cm. and weight 49 kg. The respiratory exchange was measured by means of the Zuntz-Geppert apparatus, and all experiments were with the subject in the post-absorptive condition.

The basal value was first obtained in one or two periods of observation.

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[1] Schuman-Leclerq: Wiener klin. Wochenschr., 1901, p. 237.
[2] Bergmark: Skand. Arch. f. Physiol., 1915, 32, p. 362
[3] Reach: Arch. f. exp. Path. u Pharm., 1902 47, p. 231.

These periods were usually of short duration. Four experiments were made in which the respiratory exchange was measured for several hours without the ingestion of sugar. In general, there was slight, if any, alteration in the respiratory quotient, the tendency being towards a fall. The total oxygen consumption likewise showed no material changes, although at times there were wide variations. The ingestion by mouth of 60 grams of dextrose in 120 to 200 c. c. of water raised the respiratory quotient from 0.79 to 0.87 in less than 2 hours after ingestion. In another case, it raised the quotient from 0.72 to 0.82 in about 2 hours. When the sugar was given by rectum, in one experiment the respiratory quotient before injection was 0.81, and 2 to 2½ hours afterwards the quotient was 0.84. In another observation, the quotient before the injection was 0.86, but fell to 0.80; after the injection of sugar it rose to 0.88 and 0.87 in a little over 2 hours. In the third experiment, there was no rise in the respiratory quotient. The author concludes that there is a slight absorption of dextrose by rectum, although it is not so rapid and complete as when given by mouth. Glycosuria did not occur in any case.

In addition to the respiration experiments, he studied the fermentation of the sugar solution by determinations made on the feces. The feces were moistened with water and a similar quantity of a 6 per cent solution of sugar was mixed with them. An aliquot of this was filtered and diluted 10 times and the sugar determined in the filtrate. Then a second quantity of like size was incubated, and after 3 hours the sugar was determined in the same way. In the first case the feces were obtained from a patient with diarrhea, and 16 per cent of the material disappeared; in the second case the individual was in ordinary health, and 5 per cent disappeared. Reach also made 2 experiments with the feces of a dog in which the material that disappeared amounted to 0 and 2 per cent, respectively. He believes that the absorption of carbohydrate can not be determined with accuracy from the amount remaining in the stools because of the possibility of decomposition in the intestine.

*Deucher, 1903.*—One experiment with a patient is reported by Deucher,[1] in which 5 portions of dextrose, each of 40 grams in 500 c. c. of water, were given by rectum on one day, or 200 grams of sugar in all. To 3 portions 10 drops of tincture of opium were added and to another 30 drops of tincture of opium. The absorption of the individual enemas varied from 72 to 85 per cent; the total absorption during 19 hours was 155 grams, or 77 per cent of the sugar given. The next day he gave 3 injections, each of 30 grams of dextrose in 300 c. c. of water. No stool was passed until the following day; no sugar was found in either the feces or the urine.

*Zehmisch, 1903.*—In giving the results of a 2-day experiment on himself, Zehmisch[2] points out that most of the previous work in rectal feeding has been done with single food materials and not on a combination, and it was his purpose to determine how much of a mixed enema could be absorbed by the rectum and colon. For the injection he prepared an emulsion made of 14 eggs, 1,400 c. c. of milk, 140 grams of dextrose, and 7 grams of salt. This was made up to a volume of 2,040 c. c. Six portions, each of about 250 c. c., were measured and stored on ice. This material contained in all 152.3 grams of carbohydrate, of which the greater part was dextrose. The feces were collected for the two days of the experiment and it was found that 49.4 grams of carbohydrate were unabsorbed, thus indicating that 102.9 grams had disappeared, or 67.5 per cent of the total amount injected.

*Stölting, 1904.*—The difference in the absorption of various sugars, partic-

[1] Deucher: Correspondenzbl. f. schweiz. Aertze, 1903, p. 41.
[2] Zehmisch: Ausnutzung von Nährklystieren, Diss., Halle, 1903.

ularly cane sugar, glucose, and milk sugar, was studied by Stölting[1] in experiments upon himself. In the morning a cleansing enema was taken, and an hour afterwards 250 c. c. of a sugar solution, warmed to body temperature, was passed through a rubber tube into the intestine for 30 to 40 cm. After 2 hours the material was evacuated. To remove the sugar remaining in the intestine, he passed in a liter of water and then let it flow out by simply lowering the tube. Three experiments were made with dextrose in which 25, 33.4, and 53 grams, respectively, were given, each portion in 250 c. c. of water. In the first experiment, 200 c. c. of fluid were rejected after 2 hours, with a concentration of 3.8 per cent, in contrast to the 10 per cent solution introduced. No sugar was found in the liquid from the final cleansing enema. The absorption was 17.4 grams, or 70 per cent. In the second experiment, 187 c. c. were passed after 2 hours, and this contained 5.2 grams of sugar, with a concentration of 2.8 per cent. The water from the wash-out contained 1.7 grams. The absorption was 27 grams, or about 79 per cent. In the third experiment the material which was rejected after 2 hours contained 23.8 grams of sugar, with a concentration of 7.9 per cent, in contrast to the concentration of the solution injected of slightly over 20 per cent. The liquid from the wash-out contained only 0.9 gram, so that the total sugar unabsorbed was 24.7 grams, with an absorption of 28.1 grams, or 53 per cent.

*Arnheim, 1905.*—In 4 experiments with a diabetic patient, Arnheim[2] introduced from 35 to 50 grams of dextrose in a 30 per cent solution. The observations were scattered over a period of 5½ weeks. At the beginning of the period, the patient was eliminating large quantities of sugar and had acidosis, and excreted sugar practically the entire time of observation. The upper part of the intestine was separated from the lower by means of a dilatable tampon, so that a section of about 8 to 10 cm. at the lower end was available for the absorption of the sugar solution. After the first experiment, in which 35 grams were given in a 30 per cent solution, there was a slight increase in the sugar elimination (6 grams), but this increase did not correspond to the amount of the injection. The acidosis also decreased and disappeared on the second day following. At the time of the second experiment the patient was on a strict diet and the urine sugar-free. He was given 50 grams of dextrose, and after 5 hours 3 grams were recovered. On the 2 succeeding days there was no sugar elimination and the acidosis disappeared on the second day. About a week later, when the patient was again eliminating sugar, with 40 grams of carbohydrate in the diet, he was given 50 grams of sugar by rectum, and instead of rising the sugar elimination fell and acidosis decreased. Twelve days later another 50 grams of dextrose was given, with no increase in sugar elimination. The author believed that the greater part of the sugar was utilized by the organism, because only a small part of the injected sugar was recovered in the feces and there was no increase in the sugar eliminated in the urine. He considered this to be substantiated by the decrease in the acidosis, but was uncertain as to whether the sugar was utilized, because in its absorption it did not pass through the liver or because the sugar was absorbed slowly.

*Bingel, 1905.*—Four diabetics were used as subjects by Bingel[3] in a study of the elimination of sugar and the acetone-diacetic acid reaction after the rectal injection of a dextrose solution. A diet was given the subjects to bring them to a constant sugar elimination.

With case I the elimination of sugar was approximately 70 grams per day.

[1] Stölting: Ueber den Wert verschiedener Zuckerarten als Bestandteil von Nährklystieren. Diss., Halle, 1904.
[2] Arnheim: Zeitschr. f. diät. u. physikal. Therapie, 1905, 8, p. 75.
[3] Bingel: Die Therapie der Gegenwart, 1905, p. 436.

On the third day 35 grams of dextrose were given in 100 c. c. of distilled water and an attempt was made to exclude the upper part of the large intestine by means of a tampon, as Arnheim had done. The patient was unable to retain the enema longer than 1½ hours. The stool contained 31 grams of sugar, so that apparently only 4 grams were absorbed. The next day 45 grams were given in 100 c. c. of water according to the same method. This amount was retained for only 45 minutes and rejected, there being 42.5 grams of sugar in the stool. Bingel thereafter injected the sugar without attempting to separate the upper and lower parts of the intestine, 30 grams and 50 grams of sugar being given to the subject. There was no increase in the sugar elimination, and no change in the diacetic acid reaction.

With case II, the sugar elimination was 69 grams at the beginning and later fell to 36 grams; then 50 grams of sugar were given by rectum, but the sugar elimination did not increase. Similarly, rectal feeding was used at intervals, over a period of 10 days and the sugar elimination gradually decreased to 4.5 grams. The author says that the absence of sugar in the urine after giving it by rectum was not due to better utilization, but to an increase in tolerance. Two other patients were treated in a similar manner, as much as 60 grams of dextrose per day being given rectally without apparent influence upon the sugar elimination.

Believing that the disappearance of sugar was partly due to fermentation, he made several experiments in an attempt to demonstrate this. In one, 30 grams of sugar in 300 c. c. of a salt solution were fermented with feces 5 hours and there still remained 19.5 grams of sugar; in another experiment with 50 grams of sugar, there still remained 36 grams. He concludes that fermentation may play a rôle, but is uncertain whether the action is the same in the intestine as in a fermentation experiment. The nitrogen elimination was not apparently influenced in any way by the rectal ingestion of sugar. He concludes that as the acidosis was not reduced, there is no direct proof that the sugar is better utilized and believes that the use of rectal injection of dextrose in diabetes is problematical.

*Hausmann, 1905.*—Hausmann[1] undertook to prove or disprove the work of Stölting. (See p. 6.) No food was given the evening before, and on the morning of the experimental day a cleansing enema was taken. About 1 hour later the experimental enema was given. Hausmann used a soft intestinal tube a few centimeters in length; the volume of the injection was always about 250 c. c., and the enemas were retained for about 2 hours, except when peristalsis started. He used 1 or 2 liters of water for washing out the sugar remaining in the intestine. The main purpose of the experiments was to compare the absorption and the subjective impressions of the subjects with dextrose with those which were obtained with cane sugar and milk sugar. Only the experiments with dextrose are considered here.

In the two experiments with a 10 per cent dextrose solution, the highest absorption was 79 per cent of the total amount injected; with a 15 per cent solution the highest absorption was 60 per cent. The largest amount of dextrose absorbed was 24 grams. Two experiments with a 20 per cent concentration were made. In one the enema was expelled after 45 minutes; the sugar elimination was not determined. In the other experiment, the solution was retained 1 hour; 21.3 grams or 39.9 per cent of the dextrose was absorbed. In the second series, 10 per cent of alcohol was added to a 10 per cent dextrose solution; the highest absorption in three experiments was 76 per cent, thus indicating no increase in absorption due to the addition of alcohol. Two experiments were made with a 15 per cent dextrose solution

[1] Hausmann: Experimentelle Untersuchungen über die Ausnutzung verschieden zusammengesetzer Zuckerclysmen. Diss., Halle, 1905.

to which 1 per cent of sodium chloride was added; this made practically no difference in the absorption, either in amount or in per cent.

Studies were likewise made with solutions of various temperatures. With a 15 per cent dextrose solution at 39° C., the absorption was 59 per cent of the total, while with the same concentration, but a temperature of 41.5° C., the absorption was 70 per cent of the total. The amounts injected and the amounts absorbed were fairly comparable to those which were used in the study reported in this monograph.

*Heile, 1905.*—In experimental observations upon absorption in the small and large intestines, Heile[1] conducted a number of experiments with a glucose solution on a dog which had been operated upon to exclude the small from the large intestine, and also with a patient on whom an operation had been performed in such a way as to produce an *anus prœternalis*. This made available the lower section of the large intestine which could be used for absorption experiments. Two experiments were made with the patient. In one an injection was given of 140 c. c. of a 9.3 per cent solution, containing 13.6 grams of glucose. It was retained an hour. The material from the wash-out contained 11.77 grams of sugar, with a consequent absorption of 1.83 grams. With 165 c. c. of a 16.4 per cent solution, containing 27.1 grams, the absorption was but 5.9 grams in the same time. There were three experiments with the dog. The volumes of the injection were, respectively, 77, 70, and 77 c. c., in concentrations of 5.0, 5.1, and 8.3 per cent. The absorption was 0.87, 1.16, and 1.36 grams. Heile points out that the absorption with the man was extremely small, and he does not believe it to be of much significance with rectal feeding. The values for the dog were relatively much better.

*Orlowski, 1905.*—The effect of rectal injection of dextrose solution upon the sugar elimination of diabetics was also studied by Orlowski.[2] The patients were put on a constant, usually carbohydrate-free diet, and when the sugar elimination in the urine had reached an approximately constant value, they received by rectum at first 50 grams of dextrose and on other days double this quantity. For comparison of results, a similar quantity of sugar was given by mouth. An examination of the stools after the enemas brought out the surprising fact that with one exception only 50 per cent of the sugar was actually absorbed.

With case I, on a strict diet, the sugar elimination was 25 grams per day; at 10 o'clock in the morning of the next day, 50 grams of glucose were given by rectum and the sugar elimination for that day was 20 grams. The following day, with strict diet, the sugar elimination was 16 grams. On the succeeding day, 50 grams of glucose were given by mouth and the sugar elimination rose to 62 grams. The next day, with strict diet, the sugar elimination was 37 grams. On the last day, 50 grams of glucose were injected by rectum and the sugar elimination was only 33 grams. The other cases showed results of similar character, even when 100 grams were given.

The author found that sugar by rectum was not effective in the reduction of the ammonia elimination or of the acidosis as indicated by the acetone elimination. He believes that some of the sugar disappears by bacterial decomposition, but does not consider that this explains all the results. He does not believe that the use of sugar rectally with diabetics is of great value, because it is not effective in reducing the acidosis and it is difficult for the diabetics to tolerate it. A theoretical comparison of the sugar tolerance of diabetics with oral and rectal introduction offers much of interest, but Orlowski was unable to follow the subject further.

[1] Heile: Grenzgebeite d. Med. u. Chirurg., 1905, 14, p. 474.
[2] Orlowski: Zeitschr. f. diät. u. physikal. Therapie, 1905, 8, p. 481.

*Satta, 1905.*—In an extensive study upon acidosis and acetonuria, Satta[1] made an experiment in which dextrose was injected to observe the effect upon the acetone excretion. The first day was a fasting day and then two days followed with the subject otherwise fasting, in which 150 grams of dextrose were given by rectum each day. On the fourth day, 240 grams of cane sugar were given by mouth. The elimination of acetone on the first day was 0.8 gram; on the two succeeding days, 0.5 and 0.3 gram, respectively, and on the fourth day, 0.06 gram. The ammonia excretion was 0.5, 0.7, 0.5, and 0.4 gram for the series of 4 days. The author concludes that this experiment indicates no difference between the two methods of taking the sugar, by mouth or by rectum, as to the depression or prevention of acetonuria. One should note, however, that in one case, 150 grams of dextrose were given and in the other 240 grams of cane sugar. The dextrose given by rectum apparently prevented an increase in the acidosis. The ferric-chloride reaction on the second day of the rectal injection was negative; consequently the acidosis did not increase during the fasting.

*Rosenfeld, 1907.*—In a discussion of the method of oxidation of sugar, Rosenfeld[2] reports the percentage of glycogen in the liver in several experiments with a phlorizinized dog in which the dextrose was introduced in three ways — by mouth, by rectum, and by vein. The greatest deposit of glycogen was after the introduction by mouth, the precentage in the liver varying from 3.7 to 7 per cent. The next largest average was when the dextrose was introduced by rectum, the percentage varying from 0 to 8.3 per cent, while by vein in 4 out of 7 cases there was hardly a detectable amount. Rosenfeld concludes that with introduction by mouth, the sugar is oxidized by way of the liver, while with introduction by vein and by rectum it travels in a non-hepatic path. Accordingly, dextrose, when introduced into the body, may be oxidized either by passing through the glycogen stage or without glycogen formation. In discussing rectal alimentation, many writers have quoted these experiments as an explanation of the differences between the two methods of feeding by mouth and feeding by rectum.

*Boyd and Robertson, 1906.*—Boyd and Robertson[3] made observations on 6 and 7 days upon the absorption of a mixed enema given to 6 patients. The mixed enema contained peptonized milk, eggs, salt, dextrose, and water. The amounts of dextrose used in the enema varied on the average from 38 to 88 grams and the absorption from 38 to 81 grams. The total energy-content of the dextrose varied from 151 to 332 calories.

*Rosenfeld, 1909.*—In connection with some studies on the treatment of diabetics, Rosenfeld[4] introduced glucose by rectum. With one patient who was eliminating 98 grams of sugar in the urine per day, he added 50 grams of dextrose to the diet by rectum on two days. The sugar elimination on the first day was 100 grams, or practically no increase, and on the second day the output actually decreased to 84 grams. Thus the sugar elimination was apparently not affected by the rectal injection of 50 grams of sugar.

*von Halász, 1910.*—An interest in the absorption of the various sugars and their possible splitting before absorption led von Halász[5] to make experiments on individuals from 15 to 39 years of age who were either neurasthenics or epileptics, but who were otherwise normal, especially as to the stomach and the intestinal canal. The experiments were always made in the forenoon, subsequent to a lukewarm enema and urination. The enema of sugar

[1] Satta: Beiträge z. chem. Physiol. u. Pathol., 1905, 6, p. 376.
[2] Rosenfeld: Berl. klin. Wochenschr., 1907, 44, p. 1663.
[3] Boyd and Robertson: Scottish Med. and Surg. Journ., 1906, p. 193.
[4] Rosenfeld: Berl. klin. Wochenschr., 1909, p. 957.
von Halász: Deutsch. Arch. f. klin. Med., 1910, 98, p. 433.

solution was given by means of a soft rubber tube, 30 cm. long, which was inserted 15 to 20 cm. into the intestine, with the open end of the tube attached to a glass funnel. The sugar solutions were made up with distilled water, had always a volume of 500 c. c., and varied in concentration. von Halász generally used 10, 20, and 30 per cent solutions, and occasionally a 40 per cent solution. He added 7 to 8 drops of tincture of opium to the sugar solution to assist the patients to overcome the tendency towards tenesmus. He believes that this amount is sufficient to lessen peristalsis, but too small to influence the absorption. Both the stools and urine were collected for 24 hours after the experiment and tested for sugar, the urine mainly by polarizaton.

In the series with dextrose, there were 14 observations on 6 subjects in which the quantity of dextrose introduced varied in weight from 49 to 195 grams, and the concentration from 10 to 40 per cent. The time of retention varied from 2 hours to 10½ hours. In one case there was no defecation for 38 hours. The absorption ranged between 10 grams and 144 grams. The urine was sugar-free the entire time. The absorption of sugar was not only absolutely but relatively more intense for the solutions with the highest concentrations. Thus, on the average, 8 grams per hour were absorbed from a 10 per cent solution as compared with 25 grams per hour from a 30 to 40 per cent solution; the absorption was most active in the first period following the giving of the enema.

This investigator also made experiments with levulose. There were 7 experiments completed with 4 subjects in which the solution had concentrations of 10 to 20 per cent. An attempt was also made to give levulose in a 30 per cent solution, but the subject was unable to retain it. The amount of sugar introduced varied from 49 grams to 98 grams. The amount absorbed varied from 30.8 grams to 49.6 grams. The 24-hour urine collected in connection with the experimental days was sugar-free. von Halász points out that levulose solutions are not so well borne as dextrose, but here again the rate of absorption was greater with the more concentrated solution than with the dilute. For example, with the 10 per cent solution the average absorption was 9.3 grams per hour, while with a 20 per cent solution, there was an absorption of 38.4 grams per hour. von Halász also conducted experiments with other simple sugars as well as disaccharides and, in summarizing, notes that the absorption of levulose is relatively most rapid, with dextrose next in order.

*Gompertz, 1910.*—In order to determine whether rectal absorption is effective, Gompertz[1] gave injections of potassium iodide, sodium chloride, and solutions of dextrose. When potassium iodide was dissolved in 100 c. c. of water and injected, he detected iodine in the urine and saliva in from 8 to 25 minutes. The sodium-chloride experiments were made over a period of several weeks. He found that the absorption was almost as quantitatively complete as by oral administration, and there was a marked increase of sodium chloride in the urine but only a trace in the feces after an injection of 10 grams. The dextrose experiments were made upon a patient with pancreatitis. The solutions were given over a period of 2 weeks; the analyses were made by Underhill. Injections were carried out at the rate of 500 c. c. during 5 hours, followed by a rest of 1 hour. The concentrations used varied from 3 to 15 per cent; the amounts given varied from 60 to 300 grams, and the amounts absorbed from 43 grams to 193 grams. In no instance did alimentary glycosuria occur. Gompertz believes that enemas composed of water, sodium chloride, and dextrose are rational.

*Jacobsohn and Rewald, 1911.*—It was the custom in Klemperer's clinic to

[1] Gompertz: Yale Med. Journ., 1910, 17, p. 240.

give rectally 12 grams of glucose with 12 grams of alcohol in 300 c. c. of water three times daily. Jacobsohn and Rewald[1] studied the absorption of alcohol and glucose in varying quantities and varying concentrations when introduced rectally. They also made fermentation experiments, using feces and solutions containing sugar and 5 per cent alcohol, and found no fermentation. The volumes injected varied from 450 to 2,000 c. c. and the time of retention from 3 hours to 18 hours. The alcohol given ranged between 22.5 and 100 grams and the sugar from 22.5 to 100 grams. Of 15 experiments in which alcohol was given, traces of alcohol were found in the feces in 6 experiments, 2.5 grams in one experiment when 92.5 grams of alcohol were given, and 5 grams in another experiment when 100 grams were given. The amount of sugar unabsorbed varied from 0 to 40 grams, and the amounts absorbed from 13 grams to 100 grams. In 7 experiments no sugar was found in the wash-out, thus indicating complete absorption. According to the author's calculations, the total energy absorbed varied from 208 to 1,310 calories.

*Lüthje, 1913.*—Experiments were made by Lüthje[2] on 10 diabetics in which injections were given of 50 to 100 grams of a sugar solution with a concentration of 5.4 per cent. Some of the experiments continued over a period of several weeks. In one case, the subject was given a vegetable day with 83 grams of dextrose. This was followed by 16 days of strict diet, with the addition of 75 grams of dextrose by mouth for 4 days, 81 grams of dextrose by rectum for 4 days, approximately 100 grams of bread for 3 days, 81 grams of dextrose by rectum for 1 day, and 50 grams of dextrose intravenously 1 day, by mouth 2 days, and by rectum on the final day. The elimination of sugar in the urine always increased when the dextrose was given by mouth and decreased when it was given by rectum. During this series the sugar elimination varied from 0 to 60 grams; the curve given by Lüthje follows very clearly the change according to the method of introduction.

A similar case likewise shows definitely that when dextrose (100 grams) was given by rectum, there was a fall in the elimination of sugar, and when it was given by mouth, there was an increase. Lüthje thought a possible explanation might be the slowness of the injection, as he used the drop method. To test this, slower oral introduction was obtained by giving the sugar by mouth at intervals during the day; but as the same difference between the two methods in the utilization of the sugar was found, he concluded that it could not be due to the slowness of absorption. This conclusion is important, as slowness of absorption by the rectal method is frequently offered as an explanation for the good tolerance by diabetics of sugar introduced by rectum.

In order to prove definitely that the sugar was actually absorbed and not fermented in the intestine, Lüthje made determinations of blood-sugar in observations on 5 subjects in which the duration of injection was from 6 to 7 hours. The quantity of sugar absorbed was from 59 to 84 grams. The cases all showed increases in blood-sugar. For example, with case M, the blood-sugar preceding the injection was 0.09 per cent, and following injection it was 0.19 per cent. With another case it rose from 0.13 to 0.23 per cent. With only one case was there no marked change. To obtain a control upon these results, Lüthje injected salt solution by the drop method for a period of 6 hours, and determined the blood-sugar at intervals, but found no change with any of the three subjects.

Another series of experiments was made with dogs, in which he injected sugar directly into the portal vein or into the femoral vein. There were 5 experiments. The duration of the injection varied from 45 minutes to 1½

[1] Jacobsohn and Rewald: Die Therapie der Gegenwart, 1911, p. 119.
[2] Lüthje: Die Therapie der Gegenwart, 1913, p. 193.

hours, and the quantity of sugar ingested ranged from 11.9 to 21.6 grams. He determined the amount of sugar excreted in the urine following these injections, and in every experiment the amount eliminated when introduced by the femoral vein was less than the amount eliminated when the dextrose was introduced directly into the portal circulation. Lüthje believes that these results open up an entirely new set of physiological questions, and he recommends very strongly the use of sugar enemas given by the drop method for diabetics.

*Mutch and Ryffel, 1913.*—The effect of rectal injection of peptonized milk and dextrose was studied by Mutch and Ryffel.[1] The subjects were children who had been operated upon for defective palate. The colon was washed out each morning after the rectal feeding. In one case 38.4 grams of glucose were given and only 0.07 gram recovered; in another case, 34.2 grams were injected and 0.34 gram recovered, showing an apparent absorption of 99 per cent in each case. Determinations were made of the nitrogen, ammonia, creatine, and creatinine in the urine. With one of the patients 30 grams of dextrose were given by rectum for 3 days and then 60 grams were injected for 4 days. When the injection was increased from 30 to 60 grams, there was a decrease from 0.26 gram of creatine per day to 0.11 gram. There was, however, no change in the acetone and diacetic reactions. The nitrogen fell from 5 grams to 2.5 grams in the change from 30 to 60 grams of dextrose by rectum.

Mutch and Ryffel come to the conclusion from this series and from others that they conducted that dextrose per rectum is as effective in reducing the elimination of creatine and nitrogen as is carbohydrate introduced by mouth, but that it is not so effective in reducing the acidosis. This suggests to them that dextrose, when absorbed by the colon, is to some extent metabolized in an unusual manner. They believe that the action of bacteria in the colon has something to do with the difference in metabolism of dextrose introduced rectally, especially as an increase in the urinary excretion of lactic acid was found in one case after dextrose had been given by rectum. While such bacterial action does not appear to be great, it is undesirable.

*von Willebrand, 1913.*—In studies made by von Willebrand[2] upon 5 cases of diabetes, from 50 to 100 grams of dextrose in a 5 per cent solution were injected by the drop method. Sugar thus introduced was much better utilized than an equivalent amount of carbohydrate in other forms taken by mouth. von Willebrand concludes that the favorable effect of rectal injection is due in part to the long time (several hours) over which the injections and absorption took place; that the sugar goes directly into the general circulation, avoiding the portal system; and that it is also possible that this method favors the deposit of sugar in the organism. In one observation in which the patient received a strict diet with the addition of 800 grams of milk and 60 grams of bread, the sugar elimination in the urine varied from slightly over 100 grams to 160 grams. The following 5 days he was given a strict diet, together with 80 grams of sugar by rectum; the sugar elimination gradually fell until it was slightly over 20 grams at the end of the 5 days.

*Goodall, 1914.*—In a discussion regarding the value of rectal alimentation, Goodall[3] reports a few experiments on the absorption of dextrose with varying concentrations. In one case he gave 500 c. c. of a 3 per cent solution, which was retained for 5 hours, followed by a rest of 1 hour, and in 24 hours, 42 to 52 grams were absorbed. With a 10 per cent solution, 157 to 163 grams

[1] Mutch and Ryffel: British Med. Journ., 1913, 1, p. 111.
[2] von Willebrand: Finska läkaresällskapets Handlingar, 1913, 55, part II, p. 412.
[3] Goodall: Boston Med. and Surg. Journ., 1914, 170, p. 41.

were absorbed, and with a 15 per cent solution, 144 to 193 grams were absorbed in 24 hours. He says that the amount destroyed by bacteria under these conditions varied between 0.5 and 1 per cent, and therefore it is possible to provide for one-third of the total energy requirement while the body is at rest. He also reports that alcohol is readily absorbed in concentrations of 5 or 10 per cent, although he gives no data. He believes that an isotonic solution of dextrose (5.4 per cent solutions) is best and reports that over 16 per cent always causes diarrhea.

*Bergmark, 1915.*—To compare the effect on acidosis, carbon-dioxide elimination, and content of sugar in the blood when dextrose was taken by rectum with that when it was taken by mouth or intravenously, Bergmark[1] made a series of experiments with himself as subject. The study included a number of absorption experiments. Early in the morning he took a cleansing enema, and an hour later a rectal injection containing 100 to 125 grams of dextrose in 1 liter of water, allowing it to flow in quickly. The enemas were retained from 1 to 5 hours. After a defecation, two wash-outs were given with 250 c. c. of water. The first was usually mixed with feces, while the second, which was analyzed for sugar, always gave negative results. The amounts of sugar absorbed in 9 experiments, with the retention time from 47 minutes to 6 hours, varied from 65 to 105 grams. Bergmark also made three experiments with 125 grams of dextrose in which the drop method of introduction was used, the injection time varying from 65 to 145 minutes. The solutions were retained from 30 to 60 minutes after the injection had been completed. The amounts of sugar absorbed varied from 80 to 87 grams.

In the series of respiration experiments, Bergmark first made 10 control experiments with himself in a post-absorptive condition. In these experiments the carbon-dioxide output per hour was determined by the Johansson method of alternation with a Sondén-Tigerstedt respiration chamber. He then carried out three experiments with 100 grams and 50 grams of glucose taken by mouth, in which the carbon-dioxide production was determined in alternate periods. After 100 grams of dextrose, the production of carbon dioxide increased 14.9 grams in 6 hours and after 50 grams it increased in the same time 7.0 grams. Bergmark then made several experiments with rectal injection of dextrose and determined the carbon dioxide as in the previous series. In two experiments combined as one the absorption of sugar was 93 and 97 grams. The total increase in carbon-dioxide production in 8 hours was about 21 grams. In another experiment with 125 grams, of which 104 grams of dextrose were absorbed, the carbon dioxide increased 11.8 grams in 4 hours. Three experiments, in which the solution was given by the drop method, also show increases in the carbon-dioxide production. In two of these the carbon-dioxide output was measured at the first, second, fourth, and fifth hours, with a total increase found of 10.2 and 11.4 grams, respectively. In the third experiment, in which measurements were made for only 3 hours, the increase was 5.7 grams. Bergmark concludes from his results that these experiments show without doubt that dextrose introduced rectally is actually absorbed.

Bergmark attempted to determine the increase in carbon dioxide after intravenous injection of dextrose solution, but these experiments were complicated both by chill and by an increase in body-temperature, so that the values are hardly comparable with other values obtained.

A study was also made upon the effect on the acetone elimination of the ingestion of sugar. The observations with sugar were preceded by several control days in which the acidosis was produced by diet and work. On practically all of these days, from 6 o'clock in the morning to 8 o'clock in the

[1] Bergmark: Skand. Arch. f. Physiol., 1915, 32, p. 355.

evening, there was a gradually increasing elimination of acetone. In a subsequent series, dextrose was given by mouth in amounts varying from 10 to 40 grams. In the two experiments with 40 grams there was a very definite lowering of the acetone excretion.

This series was followed by 7 experiments in which dextrose was introduced rectally in quantities varying from 30 to 125 grams. In most of these the acetone excretion was retarded, if not actually lowered, so that the author concludes that dextrose introduced rectally has a definite effect upon the acidosis, but that this effect is not so immediate and so marked as with similar quantities introduced by mouth. He believes that the difference between the results obtained with the two methods is not due merely to slower absorption with the rectal feeding, for in his rectal experiments with hourly injections a large amount of dextrose was absorbed. Furthermore, these results were controlled by mouth experiments in which 6 portions of 5 grams each were given at half-hour intervals, and there was likewise a definite lowering of the acetone excretion in less than 2 hours similar to that when the dextrose was given in one portion. He also considers that another explanation that is usually given for the difference between the results obtained with rectal feeding and those with mouth feeding, i. e., that it is due to the absorption of the sugar in the lower part of the intestine, so that it passes directly into the general circulation, likewise is not tenable as he believes that the solution, especially when quickly injected, passes into the upper part of the large intestine.

A few experiments were made upon the amount of sugar in the blood after dextrose injection. With 40 grams of dextrose given by mouth, the sugar-content increased from 0.10 to 0.16 per cent in one case and in another, when the glycogen supply was reduced, it rose from 0.10 to 0.20 per cent. The blood-sugar, when observed after the rectal introduction of 125 grams of dextrose, of which 65 grams were absorbed with the subject in a condition of glycogen reduction, showed no appreciable rise. After intravenous injection of dextrose, the rise in blood-sugar was more marked and immediate than when the sugar was given by mouth.

*Jahnson-Blohm, 1915.*—The effect on blood-sugar of the ingestion of dextrose by mouth or by rectum was studied by Jahnson-Blohm.[1] The subjects were 3 healthy individuals and 2 diabetics. The sugar solution had an isotonic concentration. With the healthy individuals the dextrose by mouth was given both in one portion or divided into several portions, and by rectum in one portion or by the drop method. With the diabetics the dextrose in both the mouth and rectal experiments was given in one portion, the amounts of dextrose being 10 grams by mouth and 30 grams by rectum. The blood-sugar was determined before the dextrose was taken, and then at intervals following the ingestion for a period of 4 hours with the normal individuals and for 2 hours with the diabetics.

When the rectal injection was given the normal subjects in one portion, the dextrose absorbed was 49.7, 31.6, and 46.6 grams. With both the normal subjects and the diabetics, the sugar by mouth produced a definite rise in the blood-sugar, this increase varying with the amount of dextrose received. When the sugar was introduced rectally, there was no rise in blood-sugar with any of the subjects. The author states that this lack of utilization explains why dextrose enemas do not produce an increase in glycosuria. He cites Rosenfeld's conclusion that the difference in utilization with oral and rectal introduction is caused by the different paths in absorption. Jahnson-Blohm, however, does not believe that a large amount of dextrose can be taken up by the veins in the lower intestine, but thinks a real difference

[1] Jahnson-Blohm: Upsala Läkareförenings Förhandlingar, 1915, 20, p. 331.

appears in the behavior of dextrose according to whether it is introduced rectally or by mouth, although his experiments offer no explanation.

*Mohr, 1917.*—Mohr[1], in Lüthje's clinic, studied the use of rectal injection of dextrose in 17 cases of diabetes; of these, 10 were classed as light cases, 3 as more severe, and 4 as severe. The solution had a concentration of 5.4 per cent and was given at body-temperature. Injection was by the drop method and generally extended over several hours. With the larger quantities, the solution was divided into several portions and quantities as high as 2 liters were given. A solution with the same concentration was given intravenously in 10 to 15 minutes. The quantity of sugar injected rectally varied from 27 to 200 grams. In those observations in which stools were recovered containing sugar, the amounts injected were from 54 to 108 grams, the quantities absorbed from these varying from 15 to 95 grams. A study of the extensive series of protocols shows that in general the dextrose injected rectally was well tolerated by the diabetics. With the light cases, usually no sugar was eliminated in the urine or, if present, there was no increase after rectal injection. The author concludes that with light cases the sugar enemas were well utilized and that they do not decrease the tolerance, that with severe cases some sugar is eliminated after rectal injection, but the quantity does not correspond to the amount introduced and the acetone excretion is slightly less. With severe cases the sugar may even disappear from the urine after rectal injection and the acetonuria be considerably lowered. This last conclusion is hardly justifiable from the protocols.

*Hári and von Halász, 1918.*—In order to find whether or not sugar is absorbed in the large intestine, Hári and von Halász[2] used determinations of the respiratory exchange rather than the wash-out method, employing dogs as subjects. To avoid the criticism that the solutions might pass into the small intestine by anti-peristalsis, the dogs were curarized, the abdomen was opened, and the small intestine was excluded by ligatures at two points below the exit into the large intestine. It was thus impossible for any material introduced into the colon to pass into the small intestine. The length of the section available for sugar absorption was usually 15 to 17 cms. That the ligatures held fast was proved by investigation after each experiment. The closure of the rectum was not complete, as, sooner or later, some fluid escaped from about the rubber tube; consequently, the investigators were not able to find the absorption by analysis.

The amounts of dextrose injected varied from 14 to 30 grams, with concentration from 15 to 30 per cent. The respiratory exchange was determined by means of the Zuntz-Geppert apparatus. With 5 of the 6 dogs experimented on, there was a definite rise in the respiratory quotient above that found in the period before the injection took place. The most marked rise in the respiratory quotient was from 0.76 in the preliminary period to 0.95 in less than 2 hours after injection. At the end of 5 hours the quotient had not returned to the initial level and there was also a strongly positive reaction for sugar in the urine. With another dog, the respiratory quotient rose from 0.82 to 0.89 in a little over 3 hours. In two other experiments, there was a positive reaction for sugar in the urine. Only one experiment was unsuccessful, its failure being due to the fact that the sugar solution leaked out around the tube leading into the rectum. The authors state that these experiments give proof that such quantities of dextrose were absorbed in the large intestine as to increase the respiratory quotient, thus indicating a combustion of sugar, and that some of the sugar escaped into the urine.

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[1] Mohr: Die Therapie des Diabetes mellitus mit Zuckerklystieren. Diss., Kiel, 1917.
[2] Hári and von Halász: Biochem. Zeitschr., 1918, 88, p. 337.

*Fleming, 1919.*—In a general study of the carbohydrate metabolism in ducks, Fleming[1] reports one experiment giving the respiratory quotient before and after the rectal injection of dextrose. The apparatus used was the Haldane respiration chamber for animals. The respiratory quotient before dextrose was given was 0.80, and 1 hour after the injection 0.91. No other details regarding the experiment are reported.

*Tallermann, 1920.*—Tallermann[2] conducted experiments in which he determined the sugar in the blood to secure evidence of the absorption of glucose. He used 60 grams of dextrose made up to 180 c. c. with normal saline solution and injected it in 10 minutes. He states there was no irritation, but his protocols show that in 2 cases the material could not be retained. With 4 cases the blood-sugar rose after the injection as follows: Case I, from 0.094 to 0.112 in 1 hour and 40 minutes; case II, from 0.044 to 0.125 in 1 hour and 40 minutes; case IV from 0.088 to 0.150 in 1 hour and 15 minutes; and case V from 0.112 to 0.138 in 1 hour. Case II was a case of functional vomiting, and the author believes that the low blood-sugar at the commencement of this experiment is probably accounted for by this condition. In about 4 hours after the injection the blood-sugar had returned to normal or below. In three cases there was no rise, but Tallermann believes that the evidence of a rise obtained from most of the determinations amply justifies the conclusion that there is actual absorption of dextrose by rectum. In considering his results, it must be noted that the concentration used by him was very high, namely, 33.33 per cent. It is surprising that there was no irritation and that most of the patients were able to retain the solution without difficulty.

*Hubbard and Wilson, 1922.*—The effect of a rectal injection of glucose solution upon the acidosis or acetonuria was studied by Hubbard and Wilson.[3] One of the authors took a diet for 4 days in which the distribution of energy was 10 per cent from protein, 10 per cent from carbohydrate, and 80 per cent from fat. Acetonuria gradually developed. The excretion of acetone on the day before the diet was taken was 0.01 gram, while on the third day of the diet it was 0.22 gram. The beta-oxybutyric acid on the day preceding the diet was 0.02 gram and on the third day of the diet 0.10 gram. On the morning of the fourth day of the diet, between $9^h\ 30^m$ a.m. and 12 noon, the subject received an enema consisting of 300 c. c. of a 5 per cent glucose solution, that is, 15 grams. The total 24-hour urine for this day showed a smaller amount of both acetone and beta-oxybutyric acid, particularly of the former. The authors say that the decrease was not so great as that caused by similar amounts of glucose when taken by mouth. In an earlier study[4] with the same distribution of calories in the diet, Hubbard and Wright found with one case after 4 days of the diet 0.9 gram of beta-oxybutyric acid and 0.5 gram of acetone. With two cases they found on the fourth day with this distribution of diet, materially higher amounts of acetone and beta-oxybutyric acid in the urine than on the fourth day when glucose by rectum was given. The authors believe that glucose is absorbed rapidly enough by rectum to decrease the excretion of acetone due to a diet high in fat.

*Lasch, 1922.*—To determine the value of sugar enemas for infants, Lasch[5] made 4 experiments with 4 children, 4 months old. In 2 of these experiments he injected by the drop method 200 c. c. of a 20 per cent solution containing 38 and 40 grams of dextrose, respectively, with tincture of opium. Only 7.4 and 7.1 grams were absorbed, that is, 20 per cent.

[1] Fleming: Journ. Physiol., 1919, 53, p. 236.
[2] Tallermann: Quart. Journ. Med., 1919–20, 13, p. 356.
[3] Hubbard and Wilson: Proc. Soc. Exp. Med. and Biol., 1922, 19, p. 292.
[4] Hubbard and Wright: Journ. Biol. Chem., 1922, 50, p. 361.
[5] Lasch: Klin. Wochenschr., 1922, p. 1936.

*Varela and Rubino, 1922.*—Varela and Rubino[1] studied the results of the injection of 100 to 200 c. c. of dextrose solutions with a concentration of over 40 per cent given to patients in the post-absorptive condition. Two hours before the beginning of the experiment, a cleansing enema was taken. The sugar solution was given by the drop method, with the duration of the injection between 1 and 2 hours. In this connection, the investigators discuss the theoretical possibility of the sugar thus injected passing into the general circulation or into the portal circulation. They believe that with the drop method there is less likelihood of the solution entering into the upper part of the intestine, and therefore not so much is likely to pass into the portal circulation, but if all the injection is given at one time, it will probably flow by the ampulla and therefore come into contact with a portion of the circulation from the intestine which connects with the portal circulation.

In 3 experiments with 100 grams, there was nearly a gram of sugar in the urine (0.7 to 1.0 gram). In one of these experiments there was no stool, consequently, the absorption is calculated as practically complete, that is, 99.2 grams. In the other experiments they recovered 31 grams and 61 grams of unabsorbed sugar from the feces and urine, thus showing an absorption of 69 grams and 39 grams, respectively. When 150 grams were injected, 52 grams were recovered with about 0.8 gram in the urine. In the case of 200 grams there was no recovery, although 4.6 grams of sugar appeared in the urine. According to observations with a concentrated dextrose solution, the details of which are not given, the greatest part of the absorption took place in approximately the first hour.

Varela and Rubino likewise determined the blood-sugar in half-hour periods for 3 hours. The greatest increase in blood-sugar was with an injection of 150 grams of dextrose, with a change from 0.08 gram to 0.13 gram 1 hour after the injection began. In all the experiments the blood-sugar increased slightly, but the authors conclude that this change indicates no special increase in glycemia and that the blood-sugar does not exceed the physiological limit. Two of the subjects who showed no measurable increase in blood-sugar with rectal feeding were given 100 grams of dextrose by mouth and a rise was found in the blood-sugar from 0.10 and 0.11 to 0.18 and 0.20, respectively, without the slightest glycosuria. They explain their results by saying that when the dextrose is injected by rectum the greater part of the sugar passes directly into the general circulation without going through the liver. The elimination of sugar in the urine, they believe, is due to the fact that the kidneys behave differently towards the sugar fed rectally from the way it acts towards that which is passing through the liver, and that its threshold value is considerably lower, their theory being that when the sugar passes through the liver, a change of unknown nature takes place either in the form of a chemical coupling or in a rearrangement within the molecule; when the sugar does not pass through the liver, the material is foreign to the body and consequently is eliminated by the kidneys.

*Rubino and Varela, 1922.*—Rubino and Varela,[2] in continuing their previous work upon the effect of the injection of dextrose solution on the blood-sugar (see above), used smaller quantities of dextrose and more dilute solutions. In the first series of 17 observations, the amounts of sugar varied from 20 grams in a 3 per cent solution to 50 grams in a 25 per cent solution, and 100 grams in a 20 per cent solution. The duration of the injection varied from one-half hour to 3 hours. The blood-sugar was determined for the most part in 1-hour intervals for 6 hours. In 14 out of the 17 observa-

[1] Varela and Rubino: Med. Klinik, 1922, p. 831.
[2] Rubino and Varela: Klin. Wochenschr., 1922, p. 2370.

tions the blood-sugar was slightly lowered. In the other 3 it rose slightly, though but one of the increases was really significant (from 0.08 to 0.13 per cent in 1 hour). In spite of variations in concentration and quantities, therefore, there was practically no change in the blood-sugar. To find whether a lengthened time of flow affected the results, they made another series of injections, in which the amounts given varied from 40 to 100 grams in a 5 per cent solution and the time of flow was from 4 to 8 hours. In 5 out of the 7 observations the blood-sugar was lowered, while in the other 2 there was a very slight rise, the greatest being from 0.10 before injection to 0.15 per cent 8 hours after the injection began. To demonstrate that actual hypoglycemia existed, they gave salt solution in three experiments and found no change in the blood-sugar. They believe that the hypoglycemia is due to a diminution in the formation of sugar by the liver, and that this lessened formation is dependent upon a special action of the sugar-regulating center, in that it is possibly affected through the formation of a sugar molecule foreign to the body when sugar is introduced rectally. This argument is in line with the report of their previous work, in which they stated the belief that the sugar molecules undergo change of a special nature in the liver.

A series of 5 experiments was made in which from 20 to 40 grams of dextrose were used in a 5 per cent solution, with the duration of flow from 1 to 4 hours. The red and white blood-cells were determined, as well as the blood-sugar. In 3 cases out of 5 there was a slight increase in blood-sugar, a decrease in white cells, and an increase in red cells, but, except in one experiment, these increases and decreases did not coincide.

In addition to these experiments with dextrose, a series of 7 experiments was made with levulose in which Rubino and Varela gave from 20 to 120 grams in solutions varying in concentration from 2.5 to 50 per cent. Determinations in periods varying from 6 to 7 hours were made of the blood-sugar and the white cells, and the red cells were also determined in several experiments. The duration of the injection varied from 1 to 3 hours. In 5 out of 7 of the experiments the greatest variation from the value before injection was minus, but in 4 cases out of the 7 there was actually an increase in the blood-sugar at some time during the period. For example, with case No. 2, the blood-sugar at the beginning was 0.10 per cent and at the end of 7 hours it was 0.16 per cent. With another case (No. 6) the preliminary value was 0.08 per cent and at the end of 3½ hours, 0.13 per cent. With case No. 7, it changed in 7 hours from 0.08 per cent to 0.12 per cent. According to their protocols, therefore, there are more instances of a rise in blood-sugar with levulose than with dextrose.

Another series of 4 experiments was made in which 40 grams of levulose in a 5 per cent solution were given in 1 hour, and comparison made of the results obtained by two methods of feeding—by mouth and by rectum. With ingestion by mouth, the figures show a slight increase of sugar in the blood, while with injection by rectum there was a slight lowering or no change. A comparison experiment with dextrose, in which 20 grams were given in a 2.5 per cent solution, indicated practically no increase with either method of feeding. To determine whether the change in the character of the sugar which they believe takes place with ingestion by mouth is due to its being mixed with secretions from the duodenum, they carried out two experiments with 40 grams of dextrose in a 10 per cent solution and a period of injection of 1½ hours, and determined the blood-sugar. In one of the experiments the solution was mixed with secretions obtained by a tube from the duodenum. In this experiment the fall in blood-sugar was 16 per cent, whereas in the experiment with no addition of secretion, the fall in blood-

sugar was 24 per cent. They conclude that the change in the sugar does not take place in the small intestine.

*Collazo, 1923.*—In a contribution upon the carbohydrate metabolism in avitaminosis, Collazo [1] published a series of experiments on 3 dogs in which sugar was injected rectally. One dog was normally nourished, another was fasting, and the third dog had been fed upon a diet without vitamines. Each of these dogs weighed about 10 kg. The three dogs were given 10 grams of glucose rectally; the concentration is not reported. Determinations of the blood-sugar showed that it fell slightly for about 2 hours, then rose in all 3 cases until at the end of 4 or 5 hours it was about 0.08 per cent higher than at its lowest point; it then began to fall. In other words, there was a slight increase in blood-sugar which took place in about 4½ hours; the normal level was just about reached with 2 of the dogs within 24 hours.

In another series of observations 50 grams of glucose were given in 150 c. c. of water to 3 dogs under the same conditions as in the first series. The injection required about 30 minutes. With the normal dog and the fasting dog the blood-sugar rose in 30 minutes, with the former from 0.10 to 0.25 per cent, and with the other from 0.15 to 0.28 per cent. With the dog fed on the diet without vitamines, this rise did not take place for 1½ hours. With all 3 dogs there was then a rapid descent to normal within 4½ to 5 hours.

## RESEARCHES WITH RECTAL INTRODUCTION OF LEVULOSE.

There were but three researches with rectal introduction of levulose. These were made by von Halász[2] and by Rubino and Varela[3] in connection with studies of dextrose injections, and the results have already been given in the dextrose section. (See pp. 10 and 19 and Schuman-Leclerq, p. 5.)

## RESEARCHES WITH RECTAL INTRODUCTION OF ALCOHOL.

Only three studies with alcohol injection by rectum should be considered in this connection. In one of these, that of Jacobsohn and Rewald,[4] a combination of dextrose and alcohol was used and the results have been reviewed in the dextrose section. (See p. 11.) The other two studies by Plantenga and by Spiro are abstracted here.

*Plantenga, 1898.*—In a dissertation published in 1898, Plantenga[5] gives a critical review of previous experimental work and likewise reports experiments of his own on the injection of protein, fat, alcohol, and carbohydrate by rectum. All of the experiments with carbohydrate were with cane sugar; consequently they have no immediate connection with the research reported in this monograph. Of particular interest in his work is the determination of alcohol absorption in the colon and large intestine of several patients. The alcohol was determined by the specific-gravity method. In one case, 180 c. c. of liquid containing 17.5 c. c. of absolute alcohol were injected; 3 hours later a wash-out of 1 liter was given; no alcohol was found in the fluid. In a second case, 26.9 c. c. of alcohol in 160 c. c. of liquid were injected, with a 1-liter enema of cold water given 45 minutes afterwards. In the 1,100 c. c. of material returned, no alcohol was found. In another case the injection was 23.3 c. c. of alcohol in 350 c. c. of fluid, with a 2-liter enema 1½ hours later; no

[1] Collazo: Biochem. Zeitschr., 1923, 136, p. 26.
[2] von Halász: Deutsch. Arch. f. klin. Med., 1910, 98, p. 433.
[3] Rubino and Varela: Klin. Wochenschr., 1922, p. 2370.
[4] Jacobsohn and Rewald: Die Therapie der Gegenwart, 1911, p. 119.
[5] Plantenga: Der Werth der Nährklystiere. Diss., Freiburg, 1898.

alcohol was present in the resulting material. To obtain further evidence that alcohol was actually absorbed, an injection of 100 grams of absolute alcohol in 2 liters of water were given to two patients, the solution being warmed to 37° C. The patients showed, 20 minutes later, symptoms of acute alcoholic intoxication.

*Spiro, 1901.*—The effect of rectal injection of alcohol upon the secretion of acid in the stomach was studied by Spiro[1] with a patient. He found that rectal injections of absolute alcohol in quantities of 10 c. c. to 200 c. c. in a sodium-chloride solution or in alcoholic beverages containing from 7 to 10 c. c. of absolute alcohol increased the acid in the stomach. The highest values were about one-half hour after the injection began, and thereafter gradually decreased.

## GENERAL SUMMARY OF LITERATURE ON RECTAL ALIMENTATION.

A survey of the literature on rectal alimentation shows that in general there are indications of a significant disappearance of dextrose from the rectum when it is introduced in solutions with concentrations up to at least 10 per cent. The absorption varies with the quantity introduced, but in general the higher the concentration of the solution or the higher the weight of dextrose actually introduced, the higher is the absorption. A number of authors have considered the possibility of the disappearance being due to fermentation, and one group of workers, Mutch and Ryffel, consider that it may be a lactic-acid fermentation. The general opinion seems to be, however, that while there is admittedly some fermentation of the dextrose in the rectum when it is introduced in the ordinary concentration, the amount which may disappear by this process is too small to account for the rapid absorption which takes place, especially in the first 2 hours, as, in general, most workers have found that the absorption is more rapid in the first hours than in the succeeding hours. That the dextrose is actually absorbed is indicated by the studies of respiratory exchange, which give, on the whole, definite results in that there is a slight increase in the carbon-dioxide elimination after the introduction of dextrose by rectum. The most marked increase was with dogs, but the experiment was conducted under somewhat unusual conditions, the dogs being curarized and the abdomen being operated upon.

The investigations with regard to blood-sugar are not wholly conclusive, because in 2 instances out of 5 negative results were found. In the sixth instance, the study by Rubino and Varela, the amount of sugar introduced was so large that the results are not comparable to those of the other experiments.

The general conclusion as to the most favorable solution to use is that a concentration of 10 per cent or under is preferable.

The evidence regarding the effect upon acidosis is conflicting, but slightly in favor of a small though definite influence.

Glycosuria was rarely found in these investigations unless the material was introduced in such a way that the path of absorption was restricted to the lower portion of the intestines.

Of unusual interest is the fact that in most of the investigations with dia-

[1] Spiro: Muench. Med. Wochenschr., 1901, p. 1871.

betics, the subjects were found to tolerate dextrose by rectum better than dextrose given by mouth. For academic interest only, it would be worth while to investigate this particular point by studies which would be thorough and continued sufficiently long to demonstrate the better tolerance with rectal injection.

The general explanation regarding rectal introduction seems to be that the path of absorption is such that it avoids the portal circulation and the substance is taken into the systemic circulation, consequently the point of utilization would be somewhat different.

With levulose there were but few investigations, and these were usually combined with the studies on dextrose. The results are, in general, the same as was found with dextrose, with no difference in effect with the levulose.

The small number of investigations upon the rectal use of alcohol or alcohol-containing materials indicates the need of study of the effect of rectal injection of this substance, particularly in view of the fact that in the past, at least, it has been a very general practice to use wine, brandy, and other alcohol-containing liquids in rectal injection.

## PLAN AND METHODS OF STUDY WITH RECTAL FEEDING OF ALCOHOL AND SUGARS.

In this study of the effect of introducing various substances into the rectum, there were two main series of observations, these being (1) the proportion absorbed of the material introduced, and (2) the respiratory exchange preceding, during, and following the period of rectal alimentation. In addition, supplementary observations were made on the effect of the rectal injection upon the volume and composition of the urine, and the percentages of elimination and concentration of the substance in the urine. For comparison, studies were also made when like substances were taken by mouth.

TABLE 1.—*Statistical data for subjects used in rectal feeding studies.*[a]

| Subject. | Age. | Height. | Body-weight. | Basal pulse-rate per min. | Basal carbon-dioxide production per min. | Basal oxygen absorption per min. | Basal heat-production per 24 hours. |
|---|---|---|---|---|---|---|---|
| | *yrs.* | *cm.* | *kg.* | | *c. c.* | *c. c.* | *cals.* |
| A | 23 | 169 | 54.0 | 64 | 157 | 206 | 1410 |
| B | 24 | 176 | 73.3 | 59 | 200 | 247 | 1712 |
| C | 24 | 178 | 69.7 | 65 | 232 | 285 | 1980 |
| D | 23 | 181 | 58.6 | .. | ... | ... | .... |

[a] The data for the basal metabolism for subjects A, B, and C, were determined in connection with this research, but are not given in detail in this publication. These average figures have been reported in a previous compilation of data. (See Harris and Benedict, Carnegie Inst. Wash. Pub. No. 279, 1919, p. 40, table C.)

The materials employed for these rectal observations were a 0.6 per cent solution of sodium chloride which was used as a control for the other studies, alcohol solutions of three concentrations (5, 7.5, and 10 per cent), and two

carbohydrates—dextrose and levulose—which were likewise given in solutions of varying densities. The amounts of alcohol used ranged between 10 and 60 grams, and the levulose between 25 and 50 grams; the dextrose was 30 grams, except for one experiment with 60 grams. The levulose, and usually the dextrose, were given in a 0.6 per cent solution of sodium chloride; the alcohol was diluted with distilled water.

The subjects were medical students, presumably in good health, designated A, B, C, and D. Subjects A and C served in all the series, but B and D were used for only a part of the observations. The age, height, weight, pulse-rate, and basal metabolism of these men are given in table 1. The basal figures given here are averages of a number of results obtained from values found in this investigation, and only those values which were secured when the subjects were in a post-absorptive condition were utilized.

Usually the man came to the Laboratory late in the afternoon, about 4 or 5 o'clock. In the beginning of the research the subjects were asked to take no food after the breakfast of that day, but in the later studies they were allowed a light lunch. In some instances they came at noon and had eaten no breakfast or nothing since breakfast. In a few cases the subjects came early in the morning and were in a true post-absorptive state.

## DETERMINATION OF AMOUNT OF ABSORPTION.

Many of the absorption studies were made in connection with the observations of the respiratory exchange, but in no way interfered with them. On his arrival at the Laboratory the man was given a cleansing enema to remove all fecal matter remaining in the large intestine and the rectum. He then went to the experimental room and lay down on a couch in readiness for the experiment. In some of the earlier studies the observations were made with the subject sitting in a semi-reclining chair. The catheter, attached to a container of the substance to be introduced, was then inserted in the rectum, and the man remained quiet for a time before the flow of the solution was begun. The period required for the complete introduction of the material varied according to the amount administered, but was usually less than one-half hour, excepting when large quantities were given. At the end of the experimental period another cleansing enema was given to remove all of the substance unabsorbed, retained for a few minutes, and then expelled. The resulting material was bottled, preserved with a layer of toluol, and subsequently determinations were made, usually in duplicate, of the amount of the solution unabsorbed in the rectum which had been removed by the cleansing enema. The Nicloux method,[1] somewhat modified, was used for the determination of the alcohol. (See p. 38.) Calculations could then be made of the amount of material introduced which had apparently been absorbed.

The determination of the unabsorbed dextrose and levulose in the cleansing enema was made by the S. R. Benedict[2] method of reduction. The method itself was standardized with pure dextrose.

[1] Nicloux: Recherches expérimentales sur l'élimination de l'alcool dans l'organisme. Détermination d'un "alcoolisme congénital". Thesis, Paris, 1900, p. 7.

[2] S. R. Benedict: Journ. Biol. Chem., 1911, 9, p. 57.

## DETERMINATIONS IN STUDY OF URINE.

The nitrogen in the urine was determined by the Folin macro-Kjeldahl method,[1] and the sodium chloride by the Harvey[2] modification of the Volhard method. The alcohol eliminated in the urine after its injection was determined by a modification of the Nicloux method. (See p. 38.)

## DETERMINATION OF RESPIRATORY EXCHANGE.

The majority of the studies of the respiratory exchange were made by the gasometer method, but in a few comparison experiments the clinical respiration chamber[3] was employed. When the former method was used, two 100-liter Tissot gasometers[4] were connected with the subject in such a way that the current of expired air could be deflected into the room or into the gasometers alternately. It was possible by this arrangement to collect the expired air continuously in periods of short duration. The valves were of the Thiry-Tissot model and made entirely of metal.[5]

In the earlier experiments the ordinary form of mouthpiece[6] was used as a breathing appliance. A difficulty arose in that the subjects, coming to the Laboratory as they did at the end of a day's activities, were more or less fatigued; consequently, when in a quiet and relaxed position, they easily became drowsy and frequently fell asleep. The mouth would then relax, with a possibility of leakage of air around the mouthpiece, thus making the measurements of the ventilation of doubtful value. This applied more especially to subject A. Beginning with November 16, 1915, therefore, the mask[7] was adopted as a breathing appliance and its successful use here has led to its general application in laboratories and in hospitals where respiration studies are made.

A comparative study[8] of respiratory exchange more recently carried out has shown that, aside from the fact that the total ventilation with the mask is slightly higher, the results obtained with it are comparable in every way with those secured with the mouthpiece or nosepiece. The application of the mask made possible continuous collection of expired air for several hours, also observations with the subject asleep, the latter being very difficult when other breathing appliances are used. With the mouthpiece, the man usually sat in a semi-reclining (steamer) chair, but with the mask he lay on a couch.

### Analysis of Expired Air.

The samples of expired air were analyzed by means of the portable form of the Haldane apparatus,[9] and occasionally controlled by analyses of out-

[1] Folin and Wright: Journ. Biol. Chem., 1919, 38, p. 461.
[2] Harvey: Arch. Intern. Med., 1910, 6, p. 12.
[3] Benedict and Tompkins: Boston Med. and Surg. Journ., 1916, 174, pp. 857, 898, and 939.
[4] Tissot: Journ. de physiol. et de pathol. gén., 1904, 6, p. 688.
[5] Thiry: Recueil des travaux de la soc. méd. Allemande de Paris, 1865, p. 57. The original valves included a short piece of large glass tubing. As this often became loose, metal was substituted. A notch on one of the rims served as a guide to the proper placing of the valve.
[6] P. Regnard: Recherches expérimentales sur les variations pathologiques des combustions respiratoires. Paris, 1879, p. 286. (See, also, Carpenter, Carnegie Inst. Wash. Pub. No. 216, 1915, p. 54.)
[7] Hendry, Carpenter, and Emmes: Boston Med. and Surg. Journ., 1919, 181, p. 288.
[8] *Ibid.*, p. 295.
[9] Haldane: Methods of air analysis. London, 2d ed., 1918, p. 47.

door air. In the greater part of the work, sodium hydrosulphite[1] was used as an absorbent for oxygen. When a large number of analyses had to be carried out at once, this reagent proved especially practical because of its power of rapid absorption. Furthermore, the solution is easily and quickly prepared for use.

### Method of Recording Respiration-Rate and Activity.

The records of the respiration-rate were obtained by the usual combination of pneumograph placed around the thorax, a Marey tambour, and a kymograph. The pneumograph around the thorax also served to record the movements of the trunk and arms, while a second combination, with the pneumograph placed around the upper part of the thighs, recorded the activity of the lower extremities.

### Method of Recording Pulse-Rate.

The heart-rate was first obtained by means of a Bowles stethoscope attached to the chest over the apex of the heart. During one of the experiments it was noted that there were minute pulsations of the pointer connected with the pneumograph around the thighs. A count of these pulsations showed that they corresponded to the heart-rate obtained from the stethoscope. Subsequently, arrangements were made to amplify the pulsations and thus obtain, in so far as practicable, in every experiment, a continuous graphic record of the pulse-rate. For this purpose a very light rod with maximum leverage was attached to the tambour; the end of this pointer was constructed in the form recommended by Bayliss.[2] When slight movements of the legs occurred, the record was interrupted.

Benedict[3] employed the pneumograph for obtaining pulse-records in connection with its use for determinations of the respiration-rate of fasting men. The pneumograph was placed over the apex beat of the heart and the pulsations were thus superimposed upon the slower movements of the pointer of the tambour which were due to respiration. In the earlier experiments of the series a graphic record was obtained, but in the majority of the observations the counts were made directly from the pulsations of the pointer. In the present research the use of the pneumograph differed from the procedure in the earlier study with fasting men in that the pulse-rates were obtained from a different portion of the body, and graphic records were secured for very long periods of time without being contaminated by other movements.

### Apparatus for Detecting Sleep.

As previously stated, very frequently the subjects became drowsy and fell asleep, even in a sitting position. After the mask was substituted for the mouthpiece and the lying position was used, it was decided to permit the subject to sleep whenever he was so inclined. This naturally resulted in experiments in which the subjects were wide awake in some periods, sound asleep in others, and in the transitional stage between these two conditions in still other periods. A method for controlling this variation in degree of wakefulness was adopted.

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[1] Durig: Biochem. Zeitschr., 1907, 4, p. 65.
[2] Bayliss: Journ. Physiol., 1912, 45; Proc. Physiol. Soc., p. xxxi.
[3] Benedict: Carnegie Inst. Wash. Pub. No. 77, 1907, p. 10.

For this purpose a signal magnet connected in series with a battery and time clock (one minute or one-half minute) was placed near enough to the subject so that he could hear it operate when the circuit was closed and opened. The man held in his hand a pear-shaped push button connected to a second signal magnet system which was independent of the first, but which recorded very near the other magnet. He was instructed to press the button whenever he was conscious that the magnet operated. Records were thus obtained of the operation of the stimulus magnet system and of the amount of the subject's response. Provided the stimulus was frequent enough, a regular response from the subject could be interpreted as an indication that the subject was wide awake. A continuous lack of response showed that he was inattentive, drowsy, or sound asleep. Comparison of these records with the course of the heart-rate supplied a definite basis for judgment as to whether the subject was really awake or sound asleep. This method of obtaining a record of the degree of wakefulness or sleep has been of great value in the interpretation of results and is strongly recommended for studies in which information as to the trend of the metabolism is desired.

### Routine of Observations of Respiratory Exchange.

After the subject came to the room in which the respiration experiment was to be made,[1] he removed such of his clothing as would interfere with the adjustment of the apparatus and the progress of the observations, and sat down in the chair or lay down upon the couch as directed. Whenever necessary for comfort, additional covering was used. The catheter was then put in position, the recording apparatus adjusted, and the mouthpiece attached or the mask applied. The preliminary period of rest varied in these experiments. With the mouthpiece it was frequently from 30 minutes to an hour in length, but when the mask was used the observations began shortly after it was applied. Previous to the injection, there were two or three preliminary periods of observation, usually about 10 minutes in duration. The solution was then administered through the catheter and further observations of the respiratory exchange made during this time, as well as after the introduction of the substance had been fully completed. In all, there were from 2 to 30 experimental periods after the beginning of the injection, with the total period of observation varying in length from 32 minutes to 8 hours 5 minutes. Records of the respiration-rate, muscular activity, and pulse-rate were simultaneously made. The analyses of the expired air gave data as to the carbon-dioxide output of the subject and the oxygen absorbed before, during, and after the rectal injection. From these the respiratory quotient for each period was calculated. The results subsequently presented give data for the oxygen consumption, respiratory quotient, and pulse-rate; for the clinical respiration-chamber experiments, the carbon-dioxide production is also given.

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[1] See routine under Determination of Amount of Absorption, p. 23.

## ABSORPTION OF ALCOHOL WHEN INTRODUCED INTO THE RECTUM.

In connection with the general study of rectal introduction of substances, observations were made of the apparent absorption of alcohol when solutions were used containing 5 per cent, 7.5 per cent, and 10 per cent of alcohol. The greater number of these observations were with the 5 per cent solution, these being 21 in number and with all four of the subjects. There were but 6 observations with the 7.5 per cent solution and 4 with the 10 per cent solution, and in these only subjects A, C, and D were used.

### ABSORPTION WITH A 5 PER CENT ALCOHOL SOLUTION.

The results of the absorption experiments with the 5 per cent alcohol solutions are given in table 2. This records the dates of the experiments,

TABLE 2.—*Absorption of 5 per cent alcohol solutions when introduced into the rectum of human subjects.*

| Subject. | Date. | Alcohol solution. | | Duration of injection. | Period injection retained. | | Wash-out. | | Apparent absorption of alcohol.[a] |
|---|---|---|---|---|---|---|---|---|---|
| | | Volume. | Weight of alcohol. | | | | Volume obtained. | Alcohol found. | |
| | 1915 | *c. c.* | *gm.* | *min.* | *h.* | *min.* | *c. c.* | *gm.* | *p. ct.* |
| A | Oct. 5 | 220 | 11.0 | 2 | 3 | 38 | 146 | None | 100.0 |
| A | Oct. 27 | 300 | 15.0 | 5 | 3 | 3 | 525 | 0.12 | 99.2 |
| B | Oct. 17 | 300 | 15.0 | .. | 4 | 24 | 250 | None | 100.0 |
| A | Oct. 12 | 320 | 16.0 | 11 | 5 | 14 | 384 | None | 100.0 |
| A | Nov. 10 | 320 | 16.0 | 25 | 3 | 27 | 385 | None | 100.0 |
| C | Oct. 29 | 320 | 16.0 | 5 | 3 | 56 | 415 | 0.11 | 99.3 |
| A | Dec. 2 | 420 | 21.0 | .. | 3 | 31 | 370 | 0.05 | 99.8 |
| C | Nov. 29 | 420 | 21.0 | 33 | 2 | 45 | 411 | 0.35 | 98.3 |
| A | Dec. 15 | 450 | 22.5 | 29 | 5 | 28 | 460 | None | 100.0 |
| A | Dec. 10 | 470 | 23.5 | 19 | 5 | 5 | 322 | None | 100.0 |
| B | Dec. 12 | 470 | 23.5 | 44 | 3 | 20 | 360 | 0.05 | 99.8 |
| C | Dec. 10 | 470 | 23.5 | 27 | 4 | 40 | 320 | 0.04 | 99.8 |
| C | Dec. 17 | 500 | 25.0 | .. | 4 | 52 | 500 | 0.25 | 99.0 |
| C | Dec. 20 | 500 | 25.0 | 22 | 2 | 3 | 355 | 4.81 | 80.0 |
| | 1916 | | | | | | | | |
| A | May 6 | [b]500 | 25.0 | 102 | 5 | 12 | [c]670<br>[c]760 | 0.08<br>None | 99.7 |
| A | May 16 | [b]500 | 25.0 | 87 | 4 | 5 | [c]1,000<br>[c]765 | 0.46<br>0.05 | 97.9 |
| A | Apr. 3 | 510 | 25.5 | 68 | 4 | 15 | [d]450<br>[d]610 | None<br>None | 100.0 |
| D | Feb. 25 | 510 | 25.5 | 47 | 3 | 17 | 340<br>350 | 0.03<br>None | 99.9 |
| D | Feb. 18 | 520 | 26.0 | 33 | 3 | 38 | 520<br>1,048 | None<br>Not done | 100.0 |
| C | May 13 | 500<br>250 | 25.0<br>25.0 | 30<br>89 | 5<br>4 | 24<br>54 | [c]930<br>[c]610 | 0.47<br>0.08 | 98.9 |
| A | Apr. 17 | 1,020 | 51.0 | 270 | 6 | 14 | 560<br>620 | None<br>Not done | 100.0 |

[a] Correction has been made for the amount left in catheter at end of injection, estimated to be 20 c. c. in volume.
[b] Solution also contained 30 grams of dextrose.
[c] 800 c. c. given. [d] 600 c. c. given.

the volumes of the solution and the weights of the alcohol, the times required for the complete introduction of the liquid, and the full periods of retention, i. e., from the beginning of the injection to the expulsion of the material following the enema given to remove the unabsorbed solution from the rectum. Data are also included for the volume of liquid obtained from this second cleansing enema or "wash-out", and the amount of alcohol which it contained, together with the percentage of alcohol which had apparently been absorbed during the time of retention of the solution.

The experiments were carried out between October 5, 1915 and May 16, 1916. The volume of the solution varied from 220 c. c. to 1,020 c. c., and the weight of the alcohol in the solution from 11 to 51 grams. These volumes and weights, however, include a small amount of the solution remaining in the catheter and connections after the completion of the injection. The residue was estimated to be about 20 c. c.; thus the amount of alcohol introduced into the rectum actually varied from 10 to 50 grams. In subsequent calculations of the amounts of alcohol absorbed, correction has been made for the alcohol which was not actually introduced. The duration of the period of injection varied from 2 minutes in the first experiment (with A on October 5, 1915) to 270 minutes in the experiment with the same subject on April 17, 1916. The amount of the solution on the latter date, however, was unusually large, being 1,020 c. c. Furthermore, it was not given continuously but in portions; consequently the total period of injection was more extended. The next longest period of injection was 102 minutes in the observation with A on May 6, 1916. In addition to the alcohol, this solution contained 30 grams of dextrose. In general, the period of injection was under 1 hour.

The time the solution was retained varied from 2 hours and 3 minutes with C on December 20 to 6 hours and 14 minutes with A on April 17. In the latter case, the entire amount of alcohol was not in the body for the full period of retention, as the injection continued over 4 hours. The time of complete retention was usually between 3 and 5 hours.

The volumes recovered from the enemas at the end of the experiment, i. e., the "wash-out", varied from 146 c. c. in the first experiment to 1,048 c. c. after the second wash-out in the experiment with D on February 18, 1916. The usual volume was from 300 to 600 c. c. The volume used for the wash-out enema at the end of the period of observation was gradually increased. In the three experiments in May 1916, a definite amount was given which was administered in duplicate, i. e., two injections of 800 c. c. each. The recovery on May 6 with subject A was 670 and 760 c. c. each; on May 16, with the same subject, it was 1,000 and 765 c. c., respectively; on May 13, with subject C, it was 930 and 610 c. c., respectively. The amount of alcohol obtained from the wash-outs varied from 0 to 4.81 grams, but was usually under 0.5 gram. In 9 experiments no alcohol was found, so that apparently there was an absorption of 100 per cent. In the other experiments this absorption varied from 99.9 to 97.9 per cent, except in one instance (the experiment with C on December 20), when it was but 80 per cent. The time of retention in this particular experiment was but 2 hours and 3 minutes from the beginning of the rectal injection, which required 22 minutes.

In conclusion, it may be stated that the alcohol in solutions containing 5 per cent of alcohol and varying from 200 c. c. to 1,000 c. c. in volume, is

almost completely absorbed when the retention is 4 hours or over, and it may be practically complete when the period of retention is 3 hours.

## ABSORPTION WITH A 7.5 PER CENT ALCOHOL SOLUTION.

The solution containing 7.5 per cent of alcohol was used for rectal injection in 6 experiments with subjects A, C, and D, in the period between March 1 and April 18, 1916. The results are given in table 3. The volume of the alcohol solution injected varied from 265 c. c. to 810 c. c., the alcohol-content ranging from 19.9 grams to 60.8 grams. With the correction of 20 c. c. for the amount left in the catheter, the actual amount available for absorption was about 1.5 grams less. The duration of the injection varied from 18 minutes with C on March 1 to 286 minutes with the same subject on April 18. The latter experiment was longer than the others in the series, a larger amount was given, and the injection was gradual. In general, the period of injection was less than one-half hour.

TABLE 3.—*Absorption of 7.5 per cent alcohol solutions when introduced into the rectum of human subjects.*

| Subject. | Date. | Alcohol solution. | | Duration of injection. | Period injection retained. | Wash-out. | | Apparent absorption of alcohol.[a] |
|---|---|---|---|---|---|---|---|---|
| | | Volume. | Weight of alcohol. | | | Volume obtained. | Alcohol found. | |
| | 1916 | *c. c.* | *gm.* | *min.* | *h. min.* | *c. c.* | *gm.* | *p. ct.* |
| C | Mar. 1 | 265 | 19.9 | 18 | 3 10 | 480<br>365 | 0.02<br>Not det'd | 99.9 |
| D | Mar. 3 | 265 | 19.9 | 26 | 4 4 | 280<br>590 | None<br>Trace | 100.0 |
| A | Apr. 10 | 350 | 26.3 | 31 | 1 0 | [b]498<br>[b]580 | 0.50<br>Trace | 98.0 |
| C | Mar. 22 | 415 | 31.1 | 20 | 3 15 | [b]610<br>[b]500 | 0.03<br>None | 99.9 |
| A | Apr. 15 | 500 | 37.5 | 27 | 1 4 | 1,080<br>670 | 4.54<br>None | 87.4 |
| C | Apr. 18 | 810 | 60.8 | 286 | 5 43 | 490<br>530 | 0.33<br>0.02 | 99.4 |

[a] Correction has been made for the amount left in catheter at end of injection, estimated to be 20 c. c. in volume.
[b] 600 c. c. given.

The range in the period of retention, which of course included the period of injection, was from 1 hour with A on April 10 to 5 hours and 43 minutes with C on April 18. In the latter experiment, as the period of injection was over 4 hours, the volume retained in the early part of the observation was considerably less than the 810 c. c. given in the whole injection.

The material obtained from the wash-out varied from 280 c. c. to 1,080 c. c., the volume usually approximating 500 c. c. or over. Two wash-outs were given in all of the experiments, with a volume as large as 600 c. c. on April 10 and March 22. The amounts recovered on these dates were 498 c. c. and 610 c. c. in the first wash-out and 580 c. c. and 500 c. c. in the second wash-out, respectively.

The amount of alcohol found in the material recovered ranged between 0 on March 3 with subject D and 4.54 grams with subject A on April 15, but in the latter case the time of retention was only 1 hour and 4 minutes.

In general, the amount absorbed was over 99 per cent, or practically complete. One may therefore draw the conclusion that the alcohol in a solution containing 7.5 per cent of alcohol in volumes up to at least 500 c. c. is completely absorbed when the period of retention is 3 hours or more.

### ABSORPTION WITH A 10 PER CENT ALCOHOL SOLUTION.

The 4 experiments with the 10 per cent alcohol solutions were made with subjects A, C, and D, in March 1916. The results are given in table 4. The volume of solution injected was, in practically all cases, 265 c. c., which contained 26.5 grams of alcohol. Allowing 0.8 gram for the residues in the flask and connections, the amount actually available for absorption was 25.7 grams. The duration of the injection was, in all cases, under one-half hour. The period of retention varied from 2 hours 30 minutes to 4 hours 5 minutes, and the apparent absorption from 99.7 to 100 per cent.

TABLE 4.—*Absorption of 10 per cent alcohol solutions when introduced into the rectum of human subjects.*

| Subject. | Date. | Alcohol solution. | | Duration of injection. | Period injection retained. | Wash-out. | | Apparent absorption of alcohol. |
|---|---|---|---|---|---|---|---|---|
| | | Volume. | Weight of alcohol. | | | Volume obtained. | Alcohol found. | |
| | 1916 | *c. c.* | *gm.* | *min.* | *h. min.* | *c. c.* | *gm.* | *p. ct.* |
| A | Mar. 6 | 265 | 26.5 | 23 | 3 45 | 655<br>[a]585<br>[c]210 | 0.05<br>None<br>0.80 | [b]99.8 |
| A | Mar. 24 | 260 | 26.0 | .. | 2 30 | 575<br>[a]435 | None<br>Not det'd | 100.0 |
| C | Mar. 8 | 265 | 26.5 | 1 | 3 13 | 220<br>[a]385<br>[c]126 | None<br>Not det'd<br>0.61 | 100.0 |
| D | Mar. 10 | 265 | 26.5 | 24 | 4 5 | 530<br>[a]437 | 0.08<br>None | [b]99.7 |

[a] Second wash-out. [b] Correction of 0.8 gram has been made for residue in flask, etc.
[c] Rinsing of flask, catheter, and connections.

The tentative conclusion drawn from these 4 experiments in which approximately 250 c. c. of a 10 per cent alcohol solution were injected is that when the solution is retained 2½ hours or more the absorption is practically complete.

## ABSORPTION OF DEXTROSE WHEN INTRODUCED INTO THE RECTUM.

In addition to the series of observations on the absorption of alcohol solutions when introduced into the rectum, a series of 11 experiments was made in which dextrose was given the subject in the same way. A 0.6 per cent solution of sodium chloride was used as the carrier in 9 of the experiments and a 5 per cent alcohol solution in the other 2. The observations were made with subjects A, C, and D. In all but one of the experiments the volume injected was 500 to 520 c. c., with a dextrose-content of 30 grams.

In the one exception (the experiment with A on April 28, 1916), the volume was 1,000 c. c., with 60 grams of dextrose. The results are given in table 5.

For the 30-gram experiments, the time of flow ranged from 29 minutes to 102 minutes and the time of retention from 2 hours 17 minutes to 6 hours 24 minutes. With the 60-gram experiment the flow was continued 254 minutes and the solution was retained 5 hours 25 minutes. In two of the 30-gram experiments three wash-outs were given, in one experiment the volume used for each wash-out being 750 c. c. and in the other 1,000 c. c. In the other experiments two wash-outs were given, usually of 800 c. c. each.

The amounts recovered from the wash-outs in the 30-gram experiments ranged from 510 c. c. to 1,075 c. c. in the first wash-out and from 470 c. c. to 1,000 c. c. in the second. The volume recovered in the second wash-out was smaller than that given in 7 out of the 10 observations, although the difference was not significant in some instances. When there was a third wash-out, the recovery was practically complete, with a slight excess in one experiment. The volumes given are large enough to obtain significant results, as Case[1] recommends that enemas of not more than 1,000 c. c. be given in most tests. With the 60 grams of dextrose, the amounts recovered in the two wash-outs were 1,020 c. c. and 797 c. c., respectively.

The sugar determined in the first enemata in the 30-gram observations varied from 1.8 grams to 11.1 grams and that determined in the second enemata from 0 in 4 experiments to 3.5 grams with subject D on May 15. Thus, for exact results, a second wash-out is required, at least with dextrose solutions of this volume and with these periods of retention. With the third wash-out, the amount determined was 0 in one 30-gram experiment and 0.9 gram in the other. There is therefore a possibility with dextrose that some sugar will still remain in the rectum even after two wash-outs. The 60-gram experiment showed 20 and 4.2 grams of sugar for the first and second wash-outs, respectively.

The amounts of dextrose apparently absorbed during the time of retention ranged in the 30-gram experiments from 17.5 to 26.3 grams, and in the 60-gram experiment it was 34.6 grams. In calculating the amount of dextrose apparently absorbed, correction was made for the volume of the solution remaining in the catheter and connections at the end of the flow. On the basis of a number of measurements under different conditions, this remainder was estimated to be 20 c. c. With the assumption that this portion was of the same concentration as the rest of the solution, a correction was made of 1.2 grams on the original 30 grams, leaving 28.8 grams as the amount actually administered. In two instances the amounts of dextrose left in the catheter were determined as 0.6 and 0.75 gram, respectively. It is possible, therefore, that the estimate of 1.2 grams is 0.5 or 0.6 gram too large.

In terms of percentage, the dextrose apparently absorbed in all the experiments, regardless of the amount administered, ranged from 59 to 90 per cent, the latter occurring with the longest period of retention and the former with the largest amount given (60 grams). It will be seen, therefore, that even in the longest observation, when the period of retention was 6 hours 24 minutes, the dextrose was not completely absorbed. In five of the eight 30-gram experiments in which the time of retention was over 4 hours, the dextrose apparently absorbed was over 70 per cent, so that to some extent

[1] Case: Medical Clinic of Chicago, Jan., 1917, 2, p. 845.

TABLE 5.—*Absorption of dextrose when introduced into the rectum of human subjects.*

| Date. | Subject. | Dextrose injected. | | Duration of injection. | Period injection retained. | Volume of wash-out. | | Amount of dextrose in wash-out. | Apparent absorption of dextrose.[a] | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Weight. | Volume of solution. | | | Given. | Recovered. | | Amount. Total. | Amount. Per hour. | Per cent. |
| 1916 | | *grams.* | *c. c.* | *min.* | *h. min.* | *c. c.* | *c. c.* | *grams.* | *grams.* | *grams.* | |
| May 4...... | A | 30 | 500 | 94 | 4 5 | 800<br>800 | 1,000<br>795 | 10.7<br>0.6 | 17.5 | 4.3 | 61 |
| May 9...... | A | 30 | 510 | 88 | 4 14 | 800<br>800 | 850<br>500 | 5.1<br>0.5 | 23.2 | 5.5 | 81 |
| May 11...... | C | 30 | 510 | 29 | 3 38 | 800<br>800 | 510<br>470 | 11.1<br>0.0 | 17.7 | 4.9 | 62 |
| May 15...... | D | 30 | 510 | 42 | 4 4 | 800<br>800 | 770<br>985 | 5.5<br>3.5 | 19.8 | 4.9 | 69 |
| May 13...... | C | 30 | 510 | 58 | 2 17 | 800<br>800 | 930<br>610 | 9.2<br>1.8 | 17.8 | 7.8 | 62 |
| 1917<br>Feb. 22...... | A | 30 | 520 | 99 | 6 24 | 900<br>900 | 610<br>840 | 1.8<br>1.2 | [b]26.3 | 4.1 | 90 |
| Apr. 17...... | C | 30 | 500 | 81 | 4 18 | 1,000<br>1,000<br>1,000 | 1,075<br>1,000<br>1,040 | 7.9<br>2.2<br>0.9 | [c]18.4 | 4.3 | 63 |
| Apr. 19...... | C | 30 | 500 | 44 | 4 53 | 750<br>750<br>750 | 950<br>750<br>710 | 8.0<br>0.0<br>0.0 | 20.8 | 4.3 | 72 |
| 1916<br>May 6...... | A | 30 | [d]500 | 102 | 5 12 | 800<br>800 | 670<br>760 | 7.9<br>0.0 | 20.9 | 4.0 | 73 |
| May 16...... | A | 30 | [d]500 | 87 | 4 5 | 800<br>800 | 1,000<br>765 | 5.2<br>0.0 | 23.6 | 5.8 | 82 |
| Apr. 28...... | A | 60 | 1,000 | 254 | 5 25 | 700<br>700 | 1,020<br>797 | 20.0<br>4.2 | 34.6 | 6.4 | 59 |

[a] Corrected for amount left in catheter at end, which was estimated to be 20 c. c. in volume and to contain 1.2 gm. of dextrose, except in experiments when the residue was actually determined.

[b] Amount in catheter and connections determined as 0.75 gm. dextrose.

[c] Amount in catheter and connections found to be 0.6 gm. at end by actual determination.

[d] 5 p. ct. alcohol solution instead of 0.6 p. ct. sodium-chloride solution.

the period of retention had a certain relation to the amount of absorption. This is borne out by the fact that the highest percentage of absorption was found after the longest period of retention and one of the lowest percentages was obtained with the shortest period.

When the time element is taken into consideration and the amount absorbed per hour is calculated, it is found that this ranged from 4.0 to 7.8 grams in the 30-gram experiments and was 6.4 grams in the 60-gram experiment. In most of the experiments it was between 4 and 5 grams per hour. The lowest amount per hour was found in one of the alcohol-dextrose experiments, with a period of retention of 5 hours 12 minutes; the highest amount per hour was for one of the sodium chloride and dextrose 30-gram experiments with the shortest period of retention (2 hours 17 minutes). The experiment with the longest period of retention (6 hours 24 minutes) gave almost the lowest amount per hour.

It is seen from the above that, even with the longest periods of retention, the absorption was never complete in these observations and that the greatest part of the absorption took place early in the retention period. Consequently, this is not a purely mathematical relationship in the sense that with additional hours of absorption the factor of division becomes larger and the amount per hour proportionately reduced. If the absorption period were 24 hours (when presumably the absorption would be complete), and this figure were used as the divisor, mathematically the amount per hour would be much smaller than any of the figures given in the table. Even in the longest period of retention the absorption of the dextrose was not complete, but the greatest rate per hour was found with the shortest period of retention, the total amount absorbed in the 2 hours and 17 minutes being 17.8 grams. In the longest period (6 hours and 24 minutes), with the same amount of dextrose injected, only 26.3 grams were absorbed, an increase of but 50 per cent although the retention period was almost three times as long. This would mean that the amount left to be absorbed was much smaller proportionally than the amount already absorbed, and the longer the period of time the smaller was the rate per hour, because the greater part of the absorption took place in the first 2 hours. Accordingly, lengthening the period of absorption would not increase but decrease the amount per hour.

Even these few experiments thus indicate that the rate of absorption is proportional to the amount of the solution present in the body, i. e., the rate with 30 grams present will be faster than with but 10 grams present. Inasmuch as these experiments with a slow rate of injection indicate very clearly that the absorption was not uniform from hour to hour, but that the greatest absorption took place at the beginning, experiments are needed to demonstrate whether, if all the solution is injected at once, the absorption will follow a definite curve, such as a "mass-law" curve, or whether it will be uniform from hour to hour. These experiments indicate that there may be an "optimum" period of retention. The question of length of period of retention before a second injection should be given is of importance when it is desirable to introduce as much nutrient material as possible. Experiments should be made with this problem as a starting-point.

## ABSORPTION OF LEVULOSE WHEN INTRODUCED INTO THE RECTUM.

Levulose, although more rarely used in rectal alimentation, was included in this research in a series of 10 experiments made with subjects A, C, and D. Like the dextrose, the levulose was given in a 0.6 per cent solution of sodium chloride. In this series there were 4 experiments with 25 grams given in 500 c. c., one experiment with 37.5 grams in 750 c. c., two with 50 grams in 1,000 c. c., and three with 50 grams in 500 c. c. The routine of the experiments was like that of the dextrose observations. The results are given in table 6.

The time of flow of the solution varied from 19 minutes with subject C on February 7 to 129 minutes with subject D on January 28. In the latter case the solution was 1,000 c. c. in volume. When a volume of only 500 c. c. was used, the maximum time of flow was 100 minutes; the minimum time with 1,000 c. c. was 99 minutes.

The time of retention for the 25 grams varied from 3 hours 17 minutes to 3 hours 32 minutes. In the one experiment with 37.5 grams, the time of retention was 2 hours 48 minutes. In the two experiments with a volume of 1,000 c. c. containing 50 grams of levulose, the period of retention was 2 hours 30 minutes and 3 hours 27 minutes respectively, while in the 3 experiments in which 50 grams were given in a volume of 500 c. c. it varied from 1 hour 29 minutes to 4 hours 35 minutes. In the experiment with the shortest period of retention (1 hour 29 minutes) the subject was obliged to urinate and consequently was unable to retain the enema.

In practically all of the experiments two wash-outs were given, or there was a defecation which interrupted the observations. The volumes of the wash-outs were not recorded, as the value of such data was not at that time recognized. When the amounts that were recovered with the defecations are excluded, those obtained from the first wash-out varied from 375 c. c. to 872 c. c.; those from the second wash-out ranged between 930 c. c. and 1,655 c. c. The amount of sugar found in the first wash-out varied from 0 to 6.5 grams and in the second wash-out from 0 in 2 cases to 3 grams in 1 case. The amount of sugar in the defecation varied from 12.0 grams with C on January 25 to 20.4 grams with D on January 28.

In the experiments when 25 grams were given and in which the times of retention were practically the same, the amount absorbed was from 16.2 grams to 21.8 grams, or 68 to 91 per cent. In the one case with 37.5 grams, there was an apparent absorption of 35.8 grams, or 98 per cent. In the two cases with 50 grams in 1,000 c. c., the absorption was 33.0 and 25.9 grams, or 67 and 53 per cent, respectively. In one of the three experiments in which 50 grams were given in 500 c. c., there was apparently complete absorption. The time of retention in this observation was longer than in any other experiment in the series, i. e., 4 hours 35 minutes. In the other two experiments, the absorption was 24.8 and 28.9 grams, or 53 and 59 per cent. Apparently the absorption of levulose is slightly greater than that of dextrose with like conditions as to the time of retention and the concentration. There are practically no experiments with dextrose comparable with those with the 50 grams of levulose, but this greater absorption of levulose seems probable from the apparently complete absorption obtained in 4 hours 35

TABLE 6.—*Absorption of levulose when introduced into the rectum of human subjects.*

| Date. | Subject. | Levulose injected. | | Duration of injection. | Period injection retained. | Volume recovered from wash-out. | Amount of levulose in wash-out. | Apparent absorption of levulose. | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | Amount. | | Per cent.[b] |
| | | Weight. | Volume of solution. | | | | | Total.[a] | Per hour. | |
| 1916 | | *grams.* | *c. c.* | *min.* | *h. min.* | *c. c.* | *grams.* | *grams.* | *grams.* | |
| Feb. 1...... | C | 25 | 500 | 100 | 3 30 | 872<br>1,225 | 4.8<br>3.0 | 16.2 | 4.6 | 68 |
| Feb. 7...... | C | 25 | 500 | 19 | 3 32 | 560<br>1,500 | 2.2<br>0 | 21.8 | 6.2 | 91 |
| Feb. 3...... | D | 25 | 500 | 63 | 3 17 | 620<br>930 | 1.2<br>2.7 | 20.1 | 6.1 | 84 |
| Feb. 11...... | D | 25 | 500 | 30 | 3 23 | 670<br>1,000 | 0.9<br>1.8 | 21.3 | 6.3 | 89 |
| Feb. 15...... | C | 37.5 | 750 | 57 | 2 48 | 745<br>1,655 | 0.7<br>0 | 35.8 | 12.8 | 98 |
| Jan. 25...... | C | 50 | 1,000 | 99 | 3 27 | [c]71<br>[d]385<br>715 | 2.0<br>12.0<br>2.0 | 33.0 | 9.6 | 67 |
| Jan. 28...... | D | 50 | 1,000 | 129 | 2 30 | [d]628<br>375 | 20.4<br>2.9 | [e]25.9 | 10.4 | 53 |
| Jan. 18...... | A | 50 | 500 | 95 | 4 35 | 425 | 0 | 48.0 | 10.4 | 100 |
| Jan. 15...... | A | 50 | 500 | 29 | 3 2 | [d]423<br>557 | 15.9<br>6.5 | [f]24.8 | 8.2 | 53 |
| Jan. 12...... | C | 50 | 500 | 54 | 1 29 | [d]190<br>530 | 15.8<br>4.5 | [g]28.9 | 19.5 | 59 |

[a] In calculating the amount of sugar absorbed, allowance is made for the solution remaining in the catheter and connections. When the amount of sugar in the residue has not been actually determined, it has been estimated that the volume of the remainder was 20 c. c., containing 1 gram of sugar with a 5 per cent solution and 2 grams of sugar with a 10 per cent solution.

[b] It is assumed that only 24 grams were available for absorption in the case of the 25-gram experiments and 49 and 48 grams in the case of the 50-gram experiments, unless the amounts of residue were determined.

[c] Drainage from the rectum after the experiment.

[d] Represents the volume of a defecation.

[e] The amount in the catheter and connections at the end of the experiment was found to be 0.8 gram.

[f] The amount remaining in the catheter and connections was 2.8 grams by actual determination.

[g] The amount in the catheter and connections was 0.8 gram.

minutes and the large proportion absorbed in the short periods of retention, such as 1 hour 29 minutes, 2 hours 30 minutes, and 2 hours 48 minutes.

There were 4 defecations, that is, in 4 observations after the injection had been completed, the subject was unable to retain the solution in the colon and rectum until the time for the first wash-out to be given. Whether or not the solution was completely expelled in this defecation there is no means of knowing, but the fact that some sugar was obtained in the succeeding wash-outs would indicate incomplete expulsion.

The volumes of the material expelled varied from 190 c. c. with subject C on January 12 after a retention of 1 hour 29 minutes to 628 c. c. with subject D on January 28, after a retention of 2 hours 30 minutes. It should be noted that this latter period of retention was but little longer than the time of flow.

When the concentrations of sugar in these 4 defecations are examined, it is found that they do not vary widely (see table 7), being 3 per cent for both C and D in the experiments on January 25 and 28, 4 per cent with subject A on January 15, and 8 per cent with subject C on January 12. In the last case the time of retention was very short, only 1 hour 29 minutes. These figures indicate that the levulose was actually absorbed more rapidly than the water in the solution, or else that there was an actual dilution of the volume in the colon and rectum, so that the concentration was lowered.

TABLE 7.—*Concentration of unabsorbed levulose in defecations.*

| Date. | Subject. | Levulose in solution. | Duration of injection. | Period injection retained. | Volume solution introduced. | Volume of defecation. | Levulose in defecation. | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | Amt. | P. ct. |
| 1916 | | *p. ct.* | *min.* | *h. min.* | *c. c.* | *c. c.* | *grams.* | |
| Jan. 25.. | C | 5 | 99 | 3 27 | 1,000 | 385 | 12.0 | 3 |
| Jan. 28.. | D | 5 | 129 | 2 30 | 1,000 | 628 | 20.4 | 3 |
| Jan. 15.. | A | 10 | 29 | 3 2 | 500 | 423 | 15.9 | 4 |
| Jan. 12.. | C | 10 | 54 | 1 29 | 500 | 190 | 15.8 | 8 |

In two of these experiments with defecations, 5 per cent solutions were introduced and in the other two 10 per cent solutions were used. The 5 per cent solutions, when calculated on a basis of the molecular weight of levulose, would give a depression of the freezing-point equal to 0.522° C., while the 10 per cent solution would give a depression of 1.044° C. The normal depression of the blood is 0.526° C., consequently, in one case, the solution was practically isotonic, while in the other case it was hypertonic. Yet in both cases the dilution was such that the concentration of the unabsorbed material was less than when it was put into the rectum. This might favor the second hypothesis that there was a dilution of the solution by the addition of water from the blood to the contents of the large intestine. On the other hand, such addition appears hardly probable, because with the shortest period of retention (1 hour 29 minutes) only 190 c. c. were obtained, whereas 500 c. c. had been injected. Furthermore, with the largest volume expelled, the time of retention (2 hours 30 minutes) corresponded very closely with the time of flow, while the difference between the amount injected into the rectum (1,000 c. c.) and the amount recovered (628 c. c.) was considerable. It would therefore seem that the lower concentration of levulose in the intestinal material was not due to dilution by water from the blood, but to the

fact that when the levulose solution was absorbed into the blood, the levulose passed in more rapidly than the water. This is somewhat contrary to the general belief that solutions usually have to be diluted before absorption can take place. In this connection it may be noted that with both dextrose and levulose the qualitative tests of the material obtained in the wash-out indicate that the absorption of the sodium chloride in the solution was complete, even when some of the sugar was found in the wash-out.

Experiments along this line are desirable for comparing the rates of absorption of the levulose when administered in solutions of sodium chloride and in water.

Sufficiently large amounts of dextrose were given for the tonicity of the solution to depress the freezing-point 0.623° C., i. e., the solution was hypertonic. Another reason why levulose is more rapidly absorbed than dextrose is the fact that the latter is normally present in small quantities in the blood, whereas levulose is not. Consequently, the blood would theoretically have a greater power for the absorption of levulose. However, the amount of dextrose in the blood is so small (but 0.12 per cent) that it may be questioned whether its presence can account for the difference in the absorption-rates of dextrose and levulose. Unfortunately the concentrations of the solutions were not identical and so the experiments are not strictly comparable. With levulose the greater the concentration or the quantity is, the greater is the absorption, this fact being apparently independent of the osmotic pressure of the blood.

## STUDIES OF URINE ELIMINATED.

In addition to the observations upon the absorption of alcohol and the respiratory exchange, supplementary studies were made of the urine eliminated. These studies included determinations of the alcohol-content, and the volume and concentration of the urine. While primarily the urines were not collected for this particular purpose, but simply as part of the routine of the respiration experiments which are reported and discussed in the latter part of this monograph, they yet supply data which throw additional light upon the action of the alcohol in the organism after its introduction by rectum.

### ELIMINATION AND CONCENTRATION OF ALCOHOL IN URINE AFTER RECTAL INJECTION (LONG COLLECTION PERIODS).

Alcohol is easily diffusible in tissues containing water and in the living organism. When introduced into the system, it appears in the body-fluids, particularly in the blood-stream, and consequently is to some extent eliminated by action of the kidneys. Since the character of the urinary secretion is dependent upon the composition of the blood, the presence of a substance in the urine indicates that it previously existed in the blood unless it was introduced directly into the bladder. Proof that a substance introduced rectally is actually absorbed would thus be supplied by its identification and quantitative determination in the body-fluids. We feel certain, therefore, that the appearance of alcohol in the urine is absolute proof that its presence there is due to its introduction into the organism. This is of importance because of its bearing on the absorption of alcohol by rectum.

*Routine of collection.*—Early in the research determinations were begun of the alcohol in the urine of the subjects. As will be described below, the Nicloux method,[1] somewhat modified, was used. Since the quantities found were significant, all of the urines were analyzed for alcohol and the amounts obtained were recorded. The usual procedure was for the subjects to urinate on their arrival at the Laboratory and again after the absorption experiment and the respiration experiment had been carried out. A statement was also obtained of the time of the last urination before the subject came to the Laboratory, but in some cases this record is deficient. The first urine collection was considered a so-called preliminary or normal sample. The second collection represented a combination of the urine secreted by the kidneys before the alcohol was given and also after its administration. Usually the period of observation before the injection was 1½ to 2 hours, so that it formed a considerable portion of the total collection period. While it is recognized that the urine thus obtained is not an unmixed urine and does not represent the actual concentration of the alcohol in the urine after the injection began, yet it was thought that such records would be of value, particularly in indicating the amount of alcohol thus eliminated.

*Method of analysis.*—The urines were usually distilled under atmospheric pressure with the addition of water and the distillates collected in small portions. The volumes of urine distilled varied between 10 and 50 c. c., according to the alcohol-content expected. The volumes of distillate collected varied from 10 to 25 c. c. and the 5 c. c. usual with the Nicloux method was employed for the determinations of the alcohol by direct titration with potassium-bichromate solution. The procedure was slightly modified from that of the original Nicloux method in the following manner: Instead of mixing in the additional bichromate as it dropped from the burette, it was dropped in, so that it rested as a layer upon the top of the alcohol-water-sulphuric acid solution. In this way the color of the added bichromate could be compared with the color of the mixture underneath it, and when such an amount had been added that there was apparently no difference in color between the lower layer and the supernatant liquid, it was considered that the titration was ended. The method was standardized by means of solutions of very dilute alcohol with a known concentration which had been determined by the density method. It is considered that the determinations are within ±5 per cent of the actual amount present in the urine.

## Urine with Rectal Injections of a 5 per cent Alcohol Solution.

By far the greater proportion of the experiments with alcohol were with 5 per cent solutions. These are gathered together in table 8, which shows the statistical data of the experiments and their results. The dates and subjects, of course, correspond with those of the previously discussed absorption experiments. The alcohol injected varied in volume from 220 c. c. to 1,020 c. c. The amount of alcohol in this volume varied from 11 grams to 51 grams. The beginning and end of the injection are also stated, except when the end-time was not recorded. The urinary data comprise the period of collection, the volume of urine eliminated during this period,

[1] Nicloux: Recherches expérimentales sur l'élimination de l'alcool dans l'organisme. Détermination d'un "alcoolisme congénital". Thesis, Paris, 1900, p. 7.

TABLE 8.—*Elimination and concentration of alcohol in urine over long periods with 5 per cent alcohol solutions introduced per rectum.*

| Date. | Subject. | Alcohol injected. Volume of solution. | Alcohol injected. Amt. of alcohol. | Time of injection. | Period of urine collection. | Volume of urine. | Alcohol in urine. Total amt. | Alcohol in urine. Per c. c. of urine. | Per cent excreted of alcohol given. |
|---|---|---|---|---|---|---|---|---|---|
| 1915 | | c. c. | grams. | | | c. c. | gram. | mg. | |
| Oct. 5 | A | 220 | 11 | 6h 14m p. m. to 6h 16m p. m. | 4h 30m p. m. to 9h 48m p. m. | 260 | 0.03 | 0.10 | 0.3 |
| Oct. 8 | A | 220 | 11 | 6 25 to 6 35 | 4 30 to 9 50 | 373 | .02 | .06 | .2 |
| Oct. 12 | A | 320 | 16 | 9 21 a. m. to 9 32 a. m. | 7 30 a. m. to 12 48 | 820 | .12 | .15 | .8 |
| Oct. 17 | B | 300 | 15 | 9 06 to ? | 7 32 to 1 23 | 420 | .04 | .09 | .3 |
| Oct. 24 | C | 325 | 16.25 | 10 39 to 10 44 | 8 40 to 1 25 | 900 | .08 | .09 | .5 |
| Oct. 27 | A | 300 | 15 | 6 49 p. m. to ? p. m. | 4 45 p. m. to 9 50 | 210 | .02 | .07 | .1 |
| Oct. 29 | C | 320 | 16 | ........ | 4 55 to 9 45 | 540 | .05 | .10 | .4 |
| Oct. 31 | B | 320 | 16 | 9h 11m a. m. to ? a. m. | 8 10 a. m. to 12 45 | 410 | .05 | .12 | .3 |
| Nov. 10 | A | 320 | 16 | 6 48 p. m. to ? p. m. | 5 20 p. m. to 10 05 | 312 | .04 | .14 | .3 |
| Nov. 16 | B | 335 | 16.75 | 8 39 to 8 49 | 6 30 to 9 55 | 725 | .03 | .04 | .2 |
| Nov. 8 | C | 320 | 16 | 6 30 to ? | 4 45 to 10 00 | 147 | .02 | .12 | .1 |
| Nov. 14 | C | 320 | 16 | 10 27 a. m. to ? a. m. | { 8 45 a. m. to 12 34 | 615 | .04 | .06 } | .4 |
| | | | | | { 12 34 p. m. to 1 30 | 505 | .03 | .06 } | |
| Nov. 18 | A | 400 | 20 | 7 03 p. m. to 7 14 p. m. | 5 50 to 9 10 | 590 | .11 | .18 | .6 |
| Nov. 24 | A | 420 | 21 | 6 45 to 6 58 | 4 40 to 9 35 | 635 | .13 | .21 | .7 |
| Dec. 2 | A | 420 | 21 | 6 44 to ? | 4 45 to 10 10 | 480 | .08 | .17 | .4 |
| Nov. 29 | C | 420 | 21 | 6 35 to 7 08 | 4 45 to 9 15 | 153 | .02 | .13 | .1 |
| Dec. 12 | B | 470 | 23.5 | 10 05 a. m. to 10 49 a. m. | { 8 10 a. m. to 11 30 a. m. | 895 | .14 | .16 } | .9 |
| | | | | | { 11 30 to 1 25 p. m. | 438 | .08 | .18 } | |
| 1916 | | | | | | | | | |
| Feb. 18 | D | 520 | 26 | 5 22 p. m. to 5 55 p. m. | 3 40 p. m. to 9 00 | 710 | .11 | .15 | .4 |
| Feb. 25 | D | 510 | 25.5 | 5 28 to 6 15 | { 3 45 to 6 56 | 670 | .13 | .19 } | .7 |
| | | | | | { 6 56 to 8 45 | 338 | .05 | .17 } | |
| Apr. 3 | A | 510 | 25.5 | 5 35 to 6 43 | 4 45 to 9 50 | 758 | .13 | .17 | .5 |
| Apr. 17 | A | 1,020 | 51 | 9 46 a. m. to 2 16 | { ? a. m. to 11 40 a. m. | 695 | .11 | .16 } | .9 |
| | | | | | { 11 40 to 4 00 p. m. | 855 | .34 | .40 } | |
| May 6 | A | [a]500 | 25 | 2 23 p. m. to 4 05 | 12 45 p. m. to 7 35 | 795 | None | ... | .. |
| May 16 | A | [a]500 | 25 | 6 30 to 7 57 | 5 45 to 10 35 | 285 | .06 | .23 | .3 |
| May 13 | C | { 500 | 25 | 10 51 a. m. to 11 21 a. m. | 9 15 a. m. to 12 50 | 1,115 | Trace | ... } | .. |
| | | { 250 | 25 | 11 21 to 12 50 p. m. | 12 50 p. m. to 4 15 | 490 | Trace | ... } | |

[a] Solution also contained 30 grams of dextrose.

the total grams of alcohol found in the urine, and the milligrams per cubic centimeter of urine, i. e., the concentration. The percentages of alcohol thus eliminated in the urine are given in the last column.

The volumes of urine eliminated varied from 147 c. c. for C on November 8 to 1,115 c. c. for the same subject on May 13. The amount of alcohol eliminated ranged from 0 or a trace in the experiments with A on May 6 and C on May 13 to 0.34 gram in the second period of collection with A on April 17. In nearly all of the urines, therefore, there was an appreciable amount of alcohol. It is rather surprising that but a trace of alcohol was found with C on May 13 when so large an amount was injected, also that none was found with A on May 6. In the latter experiment the alcohol was combined with 30 grams of dextrose in the same solution. Whether or no this had an influence upon the result can not be determined from a single negative experiment, particularly when it was found in one case with C, after a large amount of alcohol had been injected, that there was but a trace in the urine.

The results of the experiment with alcohol and dextrose suggest the desirability of further investigation on the effect of using a combination of sugar and alcohol.

The concentration of alcohol in the urine varied from 0 mg. per cubic centimeter with A on May 6 to 0.40 mg. with A in the second period of urine collection on April 17. In the experiments in which alcohol was actually found in the urine, the percentage eliminated varied from 0.1 per cent with A on October 27 and C on November 8 and 29, to 0.9 per cent in the two collections with B on December 12 and with A on April 17.

### SUMMARY OF RESULTS WITH RECTAL INJECTIONS OF A 5 PER CENT ALCOHOL SOLUTION.

These results give evidence that after the injection of 5 per cent alcohol solutions, varying in quantity from 200 to 1,000 c. c., alcohol is almost always eliminated in the urine. The amounts thus found are extraordinarily small, it is true, but it must be remembered that the times covered by the urine collections were relatively short, being on the average not over 3 or 4 hours after the injection of the alcohol. They are, however, sufficient to indicate that the alcohol introduced has passed from the rectum into the blood, and a part from the blood-stream has found its way into the kidneys, and has finally been eliminated in the urine. In general, the larger the quantity of alcohol injected, the larger is the amount of alcohol eliminated in the urine and the greater is the concentration. This is not, however, a universal rule. In some experiments in which there was a second collection period in which the urine obtained was wholly secreted after the alcohol was injected, the quantities were higher in concentration and larger in quantity than in the first collection, in which the urine was diluted with that secreted before the injection began.

### Urine with Rectal Injections of a 7.5 per cent Alcohol Solution.

In 13 experiments 7.5 per cent alcohol solutions were introduced rectally, the urines collected, and alcohol determinations made. The results are given in table 9. The subjects are the same as for the 5 per cent solutions except that subject B was not used. The amounts of alcohol solution introduced varied in volume from 265 c. c. to 810 c. c., and the urine eliminated

TABLE 9.—*Elimination and concentration of alcohol in urine over long periods with 7.5 per cent alcohol solutions introduced per rectum.*

| Date. | Subject. | Alcohol injected. | | Time of injection. | Period of urine collection. | Volume of urine. | Alcohol in urine. | | Per cent excreted of alcohol given. |
|---|---|---|---|---|---|---|---|---|---|
| | | Volume of solution. | Amt. of alcohol. | | | | Total amt. | Per c. c. of urine. | |
| 1916 | | *c. c.* | *grams.* | | | *c. c.* | *gram.* | *mg.* | |
| Feb. 28..... | A | 265 | 19.87 | 6h 25m p. m. to 6h 43m p. m. | 4h 45m p. m. to 9h 55m p. m. | 735 | 0.10 | 0.13 | 0.5 |
| Mar. 1..... | C | 265 | 19.87 | 6 05 to 6 23 | 4 45 to 9 15 | 635 | .06 | .09 | .3 |
| Mar. 3..... | D | 265 | 19.87 | 5 26 to 5 52 | 3 45 to 7 20<br>7 20 to 9 30 | 665<br>188 | .11<br>.04 | .17<br>.20 | .8 |
| Apr. 10..... | A | 350 | 26.25 | 5 11 to 5 42 | 3 55 to 6 10<br>6 10 to 10 10 | 388<br>272 | None<br>None | ....<br>.... | ... |
| Mar. 22. ... | C | 415 | 31.13 | 6 25 to 6 45 | 4 55 to 9 40 | 585 | .11 | .18 | .4 |
| Mar. 29..... | C | 510 | 38.25 | ........................... | 4 45 to 7 45<br>7 45 to 10 15 | 675<br>180 | .09<br>.04 | .13<br>.20 | .3 |
| Apr. 15..... | A | 500 | 37.50 | 3h 06m p. m. to 3h 33m p. m. | 1 45 to 4 06<br>4 06 to 6 55 | 430<br>167 | None<br>.04 | ....<br>.21 | .1 |
| Apr. 18..... | C | 810 | 60.75 | 10 22 a. m. to 3 08 | 9 20 a. m. to 4 05 | 915 | .41 | .45 | .7 |
| 1917 | | | | | | | | | |
| Jan. 20..... | A | 500 | 37.50 | 12 09 to 1 25 a. m. | 9 10 p. m. to 7 10 a. m. | 584 | .32 | .55 | .9 |
| Feb. 3..... | A | 500 | 37.50 | 12 00 p. m. to 1 22 | 8 25 to 7 45 | 760 | .43 | .56 | 1.2 |
| Feb. 15..... | A | 500 | 37.50 | 11 32 to 1 30 | 7 40 to 7 35 | 685 | .21 | .31 | .6 |
| Mar. 2..... | A | 500 | 37.50 | 9 40 to 12 12 | 7 45 to 7 13 | 780 | .23 | .30 | .6 |
| Mar. 23..... | A | 500 | 37.50 | 11 36 to 1 37 | 7 30 to 7 05 | 635 | .27 | .42 | .7 |

TABLE 10.—*Elimination and concentration of alcohol in urine over long periods with 10 per cent alcohol solutions introduced per rectum.*

| Date. | Subject. | Alcohol injected. | | Time of injection. | Period of urine collection. | Volume of urine. | Alcohol in urine. | | Per cent excreted of alcohol given. |
|---|---|---|---|---|---|---|---|---|---|
| | | Volume of solution. | Amt. of alcohol. | | | | Total amt. | Per c. c. of urine. | |
| 1916 | | *c. c.* | *grams.* | | | *c. c.* | *gram.* | *mg.* | |
| Mar. 6..... | A | 265 | 26.5 | $6^h$ $20^m$ p. m. to $6^h$ $43^m$ p. m. | $4^h$ $45^m$ p. m. to $10^h$ $10^m$ p. m. | 550 | 0.12 | 0.21 | 0.5 |
| Mar. 8..... | C | 265 | 26.5 | 6 02 to 6 03 | 4 40 to 6 55 | 790 | .08 | .10 | .7 |
| | | | | | 6 55 to 9 15 | 405 | .09 | .23 | |
| Mar. 10..... | D | 265 | 26.5 | 5 09 to 5 33 | 3 40 to 7 40 | 480 | .12 | .24 | .5 |
| | | | | | 7 40 to 9 15 | 79 | .02 | .22 | |
| Mar. 24..... | A | 260 | 26.0 | ........................... | 4 40 to 9 10 | 309 | .10 | .33 | .4 |

from 167 c. c. in the second collection on April 15 to 915 c. c. on April 18. The amounts of alcohol eliminated in the urine ranged from 0.04 gram to 0.43 gram. In two experiments with A (on April 10 and the first collection on April 15) the urine showed no trace of alcohol. The concentration of alcohol in the urine varied from 0 mg. to 0.56 mg. In general, the higher values were found in the last 6 experiments, 5 of which were with 500 c. c. of a 7.5 per cent alcohol solution and the urine collection extended over the entire night, i. e., beginning at $7^h$ $30^m$ p.m. to $9^h$ $10^m$ p.m., and ending at $7^h$ $05^m$ a.m. to $7^h$ $45^m$ a.m. The percentage of alcohol excreted in the urine varied from 0 with A on April 10 to 1.2 per cent with A on February 3.

#### SUMMARY OF RESULTS WITH RECTAL INJECTIONS OF A 7.5 PER CENT ALCOHOL SOLUTION.

When 7.5 per cent alcohol solutions, varying in volume from 265 to 810 c. c. were injected rectally, the urines voided in the subsequent 2 to 8 hours contained alcohol ranging in quantity from 0 to 427 mg., and had an alcohol concentration from 0 to 0.56 mg. per cubic centimeter of urine and a percentage elimination from 0 to 1.2 per cent. In general, the percentages excreted with 7.5 per cent alcohol solutions are not materially higher than those with 5 per cent alcohol solutions. The concentrations are slightly higher, particularly in those experiments when the urines were collected over a long period during the night. It must be noted, however, that the quantity of absolute alcohol in this case was 37.5 grams, nearly 50 per cent larger than in the majority of experiments with 5 per cent alcohol solutions.

#### Urine with Rectal Injections of a 10 per cent Alcohol Solution.

In 4 experiments 10 per cent alcohol solutions were injected rectally, the urines collected, and alcohol determinations made. The results are given in table 10. The solution injected was 265 or 260 c. c. in volume, containing 26.5 or 26 grams of alcohol. The volume of urine collected varied from 79 c. c. to 790 c. c. The amount of alcohol in these urines varied from 0.02 to 0.12 gram, the concentration from 0.10 to 0.33 milligram, and the percentage excretion from 0.4 to 0.7. In general, the concentrations were slightly higher than the concentrations with either 5 per cent or 7.5 per cent alcohol solutions in the experiments of about the same duration and with about the same quantities of alcohol.

### COMPARISON OBSERVATIONS OF ALCOHOL IN URINE AFTER ITS INGESTION BY MOUTH.

In 6 experiments alcohol was given by mouth in concentrations of 5, 7.5, and 10 per cent. In 3, 400 c. c. of a 5 per cent solution were given, in 2, 250 c. c. of a 7.5 per cent solution, and in one, 250 c. c. of a 10 per cent solution. The urines were collected in the same manner as in the preceding experiments, and the results of the analyses are given in table 11. The volumes of urine varied from 70 c. c., the second collection on December 23, to 862 c. c., the first collection for the same date. The amount of alcohol in the urine ranged from 0.01 gram to 0.25 gram. The concentration varied from 0.19 to 0.32 mg., so that, on the average, the concentrations were a little higher than those with corresponding amounts given by rectum. The percentage excretion of

TABLE 11.—*Elimination and concentration of alcohol in urine over long periods with 5, 7.5, and 10 per cent solutions given by mouth.*

| Date. | Subject. | Alcohol given. | | Time taken. | Period of urine collection. | Volume of urine. | Alcohol in urine. | | Per cent excreted of alcohol given. |
|---|---|---|---|---|---|---|---|---|---|
| | | Volume of solution. | Amt. of alcohol. | | | | Total amt. | Per c. c. of urine. | |
| 1915 | | *c. c.* | *grams.* | | | *c. c.* | *gram.* | *mg.* | |
| 5 p. ct.: | | | | | | | | | |
| Dec. 15... | C | 400 | 20 | $6^h\ 54^m$ p. m. to $6^h\ 57^m$ p. m. | $4^h\ 45^m$ p. m. to $10^h\ 25^m$ p. m. | 760 | 0.14 | 0.19 | 0.7 |
| Dec. 17... | A | 400 | 20 | 6 38 to 6 44 | 4 45 to 9 45 | 560 | .12 | .22 | .6 |
| Dec. 23... | C | 400 | 20 | 2 40 to 2 43 | 12 55 to 4 20 | 862 | .20 | .23 | 1.1 |
| | | | | | 4 20 to 5 40 | 70 | .01 | .19 | |
| 1916 | | | | | | | | | |
| 7.5 p. ct.: | | | | | | | | | |
| Mar. 27... | A | 250 | 18.75 | 5 36 to 5 37 | 3 50 to 9 15 | 455 | .13 | .29 | .7 |
| Apr. 1... | C | 250 | 18.75 | ........................ | 12 45 to 6 15 | 510 | .10 | .21 | .5 |
| 10 p. ct.: | | | | | | | | | |
| Apr. 20... | A | 250 | 25 | $10^h\ 03^m$ a. m. to $10^h\ 07^m$ a. m. | 8 30 a. m. to 4 20 | 782 | .25 | .32 | 1.0 |

alcohol in the urine varied from 0. 5 to 1.1 per cent. The average figures are thus likewise slightly higher than the averages for the preceding groups of urines when alcohol was given by rectum.

This comparison brings out the fact that even when differing methods were used for introducing the alcohol, namely, by rectum and by mouth, the concentration of the alcohol in the urine collected over a period of time was about the same in both cases and the amount of alcohol eliminated in the urine was likewise similar. This would indicate that the rate of absorption and the rate of distribution and variation in concentration from time to time are not unlike with rectal and oral introduction of alcohol. These findings are important in comparing the effects of alcohol introduced by different methods upon the respiratory exchange, the heart-rate, and the total metabolism, which are considered in discussing the results of the metabolism experiments.

## ELIMINATION AND CONCENTRATION OF ALCOHOL IN URINE AFTER ITS RECTAL INJECTION (SHORT COLLECTION PERIODS).

When alcohol was found in urine at the end of these long experimental periods in which solutions were injected by rectum, it was believed that the determination of alcohol in urines collected at intervals, with periods as short as possible, would throw some light on the metabolism of alcohol. Experiments were therefore carried out in which this was done. In most cases the subject was in a sitting position. Every 15 minutes he drank a glassful of tap-water so as to promote a free flow of urine. The urine was voided by the subject whenever possible, and consequently the lengths of the periods were influenced by several factors, viz, the influence of alcohol itself; nervous mechanism of the subject; quantity of fluid taken by the mouth; quantity of fluid injected rectally; and finally the ability of the subject to retain the solution injected rectally and at the same time relax the bladder sphincter. The last concerns most the first collection of urine after the rectal injection began and proved to be the most important factor in determining the length of this period. A number of times the subject desired to urinate, but did not do so for fear of losing the solution which had been injected.

The results of the determinations of the alcohol in urine collected in short periods after rectal injection are presented and discussed in the following pages. In table 12 details are given for each experiment of the time and amount of the injection, times of urination, length of periods of collection, total volume of urine collected in each period before and after injection, volume of urine per minute, the amount of alcohol eliminated in the urine, and the concentration, i. e., the amount of alcohol per cubic centimeter of urine.

In all, there were 9 experiments, 2 with subject A and 7 with subject C. In the 8 experiments with a 5 per cent solution of alcohol, the volume ranged between 420 and 500 c. c., except in 1 experiment, when it was 750 c. c. In the remaining experiment, 250 c. c. of a 10 per cent solution were injected. The first collection of alcohol urine was from 1 hour and 5 minutes to 2 hours and 22 minutes after the beginning of the injection, but usually inside of 2 hours.

As a rule, the observations were continued for 5 or 6 hours excluding those overnight. Detailed statistics for the experiment with A on December 15, 1915, will suffice to indicate the characteristics of the whole group, and a more general discussion of these experiments with short periods of urine collection will be given later.

TABLE 12.—*Elimination and concentration in urine of alcohol injected by rectum.*

| Subject, date, and time of urinating. | Length of period. | Time since alcohol injected. | Volume of urine. | | Alcohol excreted in urine. | |
|---|---|---|---|---|---|---|
| | | | Total. | Per minute. | Total. | Per c. c. of urine. |
| C. Dec. 2, 1915. | *min.* | *h. min.* | *c. c.* | *c. c.* | *mg.* | *mg.* |
| $5^h$ $27^m$ p. m. | 420 c. c. of 5 per cent solution. | | | | | |
| 7 40[a] | 170 | 2 13 | 118 | 6.9 | 12 | 0.10 |
| 8 01 | 21 | 2 34 | 750 | 35.7 | 76 | .10 |
| 8 50 | 49 | 3 23 | 450 | 9.2 | 24 | .05 |
| 9 40 | 50 | 4 13 | 465 | 9.3 | 0 | .... |
| 10 20 | 40 | 4 53 | 370 | 9.3 | 0 | .... |
| 11 45 | 85 | 6 18 | 280 | 3.3 | 0 | .... |
| Dec. 3, 1915. | | | | | | |
| $7^h$ $25^m$ a. m.[b] | 460 | 13 58 | 287 | 0.6 | 0 | .... |
| Total | ... | .. .. | ... | .... | [c]112 | .... |
| Average | ... | .. .. | ... | .... | ... | 0.08 |
| A. Dec. 15, 1915. | | | | | | |
| $4^h$ $43^m$ p. m.[a] | 253 | .. .. | 340 | 1.3 | ... | .... |
| 5 18 to $5^h$ $47^m$ p. m. | 450 c. c. of 5 per cent solution. | | | | | |
| 6 30 p. m. | 107 | 1 12 | 162 | 1.5 | 44 | 0.27 |
| 7 00 | 30 | 1 42 | 240 | 8.0 | 76 | .32 |
| 7 28 | 28 | 2 10 | 202 | 7.2 | 54 | 27 |
| 8 05 | 37 | 2 47 | 322 | 8.7 | 64 | .20 |
| 8 51 | 46 | 3 33 | 430 | 9.3 | 52 | .12 |
| 9 33 | 42 | 4 15 | 347 | 8.3 | 15 | 04 |
| 10 03 | 30 | 4 45 | 322 | 10.7 | 11 | 03 |
| 10 05 | 2 | 4 47 | 39 | 19.5 | ... | .... |
| 10 46 | 41 | 5 28 | 381 | 9.3 | 0 | . . |
| 11 50 | 64 | 6 32 | 448 | 7.0 | 0 | . . |
| Dec. 16, 1915. | | | | | | |
| $7^h$ $05^m$ a. m.[b] | 435 | 13 47 | 685 | 1.6 | Trace | . . . |
| Total | ... | .. .. | ... | .... | [c]316 | .... |
| Average | ... | .. .. | . . | .... | ... | 0.16 |
| C. Dec. 10, 1915. | | | | | | |
| $5^h$ $00^m$ p. m.[a] | 150 | .. .. | 140 | 0.9 | Trace | .... |
| 5 20 to $5^h$ $47^m$ p. m. | 470 c.c. of 5 per cent solution. | | | | | |
| 6 55 p. m. | 115 | 1 35 | 830 | 7.2 | 137 | 0.16 |
| 7 25 | 30 | 2 5 | 285 | 9.5 | 53 | .18 |
| 8 55 | 90 | 3 35 | 575 | 6.4 | 80 | .14 |
| 9 50 | 55 | 4 30 | 295 | 5.4 | 13 | .04 |
| 9 55 | 5 | 4 35 | 97 | 19.4 | 3 | .03 |
| 10 25 | 30 | 5 5 | 330 | 11.0 | 0 | .... |
| 11 40 | 75 | 6 20 | 540 | 7.2 | 0 | .... |
| Dec. 11, 1915. | | | | | | |
| $7^h$ $15^m$ a. m.[b] | 455 | 13 55 | 360 | 0.8 | Trace | .... |
| Total | ... | .. .. | ... | .... | [c]286 | .... |
| Average | ... | .. .. | ... | .... | ... | 0.14 |

TABLE 12.—*Elimination and concentration in urine of alcohol injected by rectum*—Cont.

| Subject, date, and time of urinating. | Length of period. | Time since alcohol injected. | Volume of urine. | | Alcohol excreted in urine. | |
|---|---|---|---|---|---|---|
| | | | Total. | Per minute. | Total. | Per c. c. of urine. |
| A. Dec. 10, 1915. | *min.* | *h. min.* | *c. c.* | *c. c.* | *mg.* | *mg.* |
| 5h 00m p. m.[a] | 180 | .. .. | 435 | 2.4 | Trace | .... |
| 5 20 to 5h 39m p. m. | 470 c. c. of 5 per cent solution. | | | | | |
| 6 36 p. m. | 96 | 1 16 | 485 | 5.1 | 112 | 0.23 |
| 7 25 | 49 | 2 5 | 370 | 7.6 | 99 | .27 |
| 8 25 | 60 | 3 5 | 495 | 8.3 | 87 | .18 |
| 9 30 | 65 | 4 10 | 565 | 8.7 | 35 | .06 |
| 10 00 | 30 | 4 40 | 318 | 10.6 | 6 | .02 |
| 10 25 | 25 | 5 5 | 220 | 8.8 | 0 | .... |
| Total | ... | .. .. | ... | .... | [c]339 | .... |
| Average | ... | .. .. | ... | .... | ... | 0.15 |
| C. Dec. 17, 1915. | | | | | | |
| 5h 00m p. m.[a] | 270 | .. .. | 518 | 1.9 | Trace | .... |
| 5 18 | 500 c. c. of 5 per cent solution. | | | | | |
| 7 40 | 160 | 2 22 | 570 | 3.6 | 92 | 0.16 |
| 8 40 | 60 | 3 22 | 498 | 8.3 | 69 | .14 |
| 9 12 | 32 | 3 54 | 190 | 5.9 | 11 | .06 |
| 9 45 | 33 | 4 27 | 250 | 7.6 | 9 | .04 |
| 10 10 | 25 | 4 52 | 290 | 11.6 | 8 | .03 |
| 12 00 | 110 | 6 42 | 1087 | 9.9 | 0 | .... |
| Dec. 18, 1915. | | | | | | |
| 7h 30m a. m.[b] | 450 | 14 12 | 655 | 1.5 | Trace | .... |
| Total | ... | .. .. | ... | .... | [c]189 | .... |
| Average | ... | .. .. | ... | .... | ... | 0.11 |
| C. Dec. 20, 1915. | | | | | | |
| ? | ... | .. .. | 79 | .... | 0 | .... |
| 6h 10m p. m. | ... | .. .. | 138 | .... | [d]25 | 0.18 |
| 6 25 | 15 | .. .. | 192 | 12.8 | 0 | .... |
| 6 27 to 6h 49m p. m. | 500 c. c. of 5 per cent solution. | | | | | |
| 8 30 p. m. | 125 | 2 3 | 1130 | 9.0 | 140 | .12 |
| 9 25 | 55 | 2 58 | 415 | 7.5 | 38 | .09 |
| 9 50 | 25 | 3 23 | 300 | 12.0 | 15 | .05 |
| 11 05 | 75 | 4 38 | 614 | 8.2 | 15 | .03 |
| Dec. 21, 1915. | | | | | | |
| 7h 30m a. m.[b] | 505 | 13 3 | 614 | 1.2 | Trace | .... |
| Total | ... | .. .. | ... | .... | [e]208 | .... |
| Average | ... | .. .. | ... | .... | ... | 0.08 |

Table 12.—*Elimination and concentration in urine of alcohol injected by rectum*—Cont.

| Subject, date, and time of urinating. | Length of period. | Time since alcohol injected. | Volume of urine. | | Alcohol excreted in urine. | |
|---|---|---|---|---|---|---|
| | | | Total. | Per minute. | Total. | Per c. c. of urine. |
| C. Jan. 15, 1916. | *min.* | *h. min.* | *c. c.* | *c. c.* | *mg.* | *mg.* |
| $1^{h}$ $55^{m}$ p. m.[a] | 325 | .. .. | 348 | 1.1 | 0 | .... |
| 2 16 to $2^{h}$ $21^{m}$ p. m. | 500 c. c. of 5 per cent solution. | | | | | |
| 3 21 p. m. | 86 | 1 5 | 325 | 3.8 | 80 | 0.25 |
| 3 55 | 34 | 1 39 | 260 | 7.6 | 60 | .23 |
| 4 25 | 30 | 2 9 | 290 | 9.7 | 48 | .16 |
| 4 45 | 20 | 2 29 | 235 | 11.7 | 23 | .10 |
| 5 15 | 30 | 2 59 | 270 | 9.0 | 16 | .06 |
| 5 45 | 30 | 3 29 | 370 | 12.3 | 10 | .03 |
| Total | ... | .. .. | ... | .... | [c]237 | .... |
| Average | ... | .. .. | ... | .... | ... | 0.14 |
| C. Jan. 18, 1916. | | | | | | |
| $2^{h}$ $13^{m}$ to $2^{h}$ $35^{m}$ p. m. | 750 c. c. of 5 per cent solution. | | | | | |
| 4 05 p. m.[a] | 120 | 1 52 | 550 | 4.6 | 190 | 0.35 |
| 5 15 | 70 | 3 2 | 550 | 7.9 | 152 | .28 |
| 6 00 | 45 | 3 47 | 425 | 9.4 | 116 | .27 |
| 7 00 | 60 | 4 47 | 620 | 10.3 | 115 | .19 |
| 8 06 | 66 | 5 53 | 665 | 10.1 | 91 | .14 |
| 9 00 | 54 | 6 47 | 660 | 12.2 | 30 | .05 |
| Total | ... | .. .. | ... | .... | [c]694 | .... |
| Average | ... | .. .. | ... | .... | ... | 0.20 |
| C. May 6, 1916. | | | | | | |
| $1^{h}$ $45^{m}$ p. m.[a] | 75 | .. .. | 73 | 1.0 | Trace | .... |
| 2 00 to $2^{h}$ $04^{m}$ p. m. | 250 c. c. of 10 per cent solution. | | | | | |
| 3 40 p. m. | 115 | 1 40 | 445 | 8.1 | 159 | 0.36 |
| 4 15 | 35 | 2 15 | 70 | 2.0 | 20 | .28 |
| 4 53 | 38 | 2 53 | 197 | 5.2 | 31 | .16 |
| 5 50 | 57 | 3 50 | 169 | 3.0 | 24 | .14 |
| 6 15 | 25 | 4 15 | 35 | 1.4 | Lost | .... |
| 6 45 | 30 | 4 45 | 204 | 6.8 | 9 | .04 |
| 7 12 | 27 | 5 12 | 255 | 9.5 | 9 | .04 |
| 7 55 | 43 | 5 55 | 94 | 2.2 | 3 | .04 |
| Total | ... | .. .. | ... | .... | [c]255 | .... |
| Average | ... | .. .. | ... | .... | ... | 0.18 |

[a] Urine passed before experiment, but not saved, at the following times: Dec. 2, $4^{h}$ $50^{m}$ p.m.; C, Dec. 10, $2^{h}$ $30^{m}$ p. m.; A, Dec. 10, 2 p. m.; Dec. 15 and 17, $12^{h}$ $30^{m}$ p. m.; Jan. 15, $8^{h}$ $30^{m}$ a. m.; Jan. 18, $2^{h}$ $05^{m}$ p. m.; May 6, $12^{h}$ $30^{m}$ p. m.

[b] Collected by subject.

[c] The proportional part of the alcohol injected which was eliminated in the urine was as follows: Dec. 2, 0.6 p. ct.; C, Dec. 10, 1.3 p. ct.; A, Dec. 10, 1.5 p. ct.; Dec. 15, 1.4 p. ct.; Dec. 17, 0.8 p. ct.; Dec. 20, 0.9 p. ct.; Jan. 15, 1.0 p. ct.; Jan. 18, 1.9 p. ct.; May 6, 1.1 p. ct.

[d] Presumably due to taking of coffee. (See p. 58.)

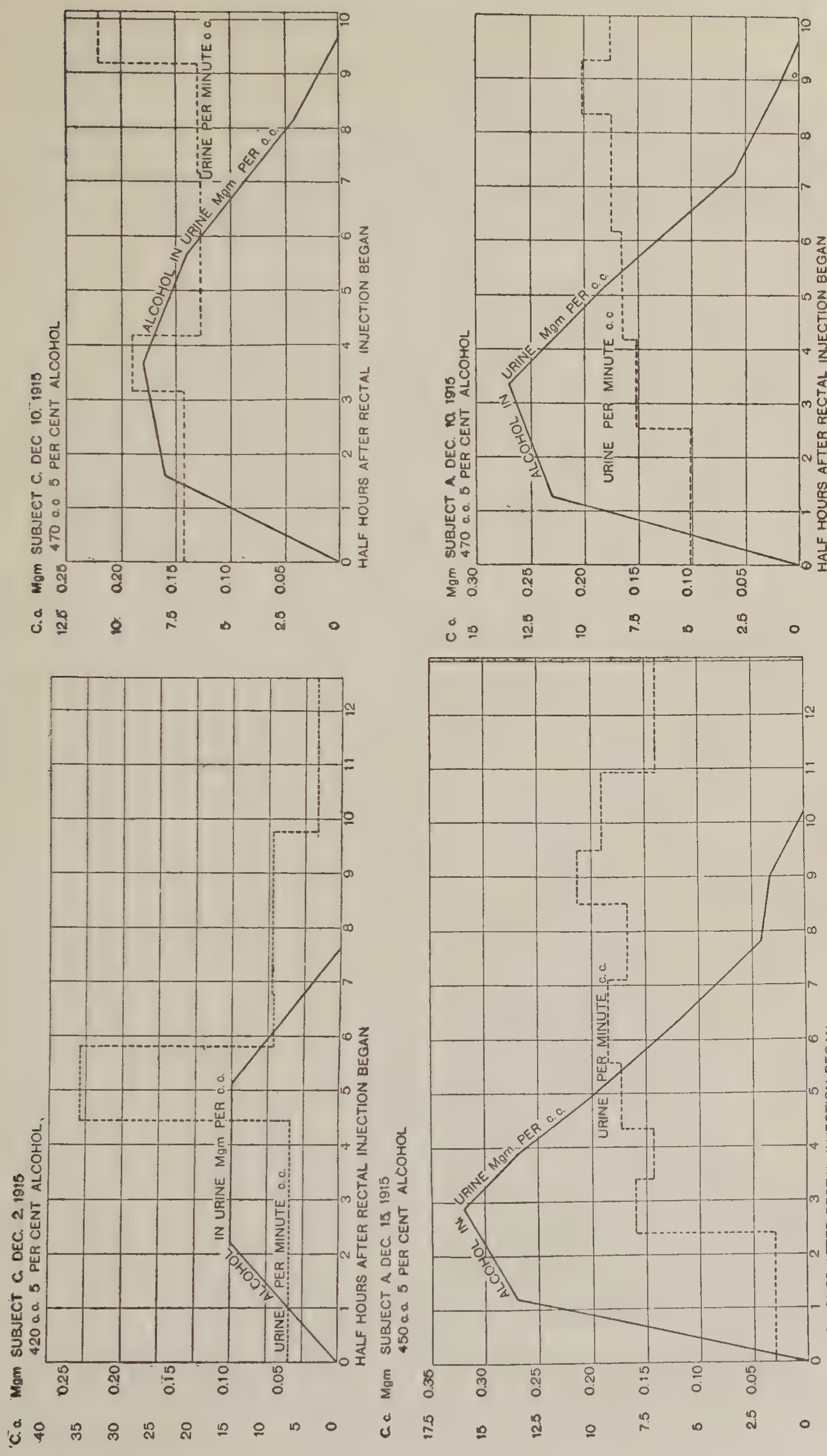


FIG. 1.—Milligrams of alcohol per cubic centimeter of urine, and volume of urine per minute, after rectal injection of 420 to 470 c. c. of a 5 per cent (by weight) alcohol solution.

*Subject A, December 15, 1915.*—Rectal injection, 450 c. c. of a 5 per cent alcohol solution. The injection was given between $5^h\ 18^m$ and $5^h\ 47^m$ p. m. and the urine was collected thereafter at short intervals. The first collection after the alcohol was at $6^h\ 30^m$ p. m. or 1 hour and 12 minutes after the solution had been given; the alcohol concentration of the urine was 0.27 mg. per cubic centimeter. The urine collected in the second period, ending at 7 p. m., 1 hour and 42 minutes after the beginning of the injection, gave the highest concentration for this day, i. e., 0.32 mg. per cubic centimeter.

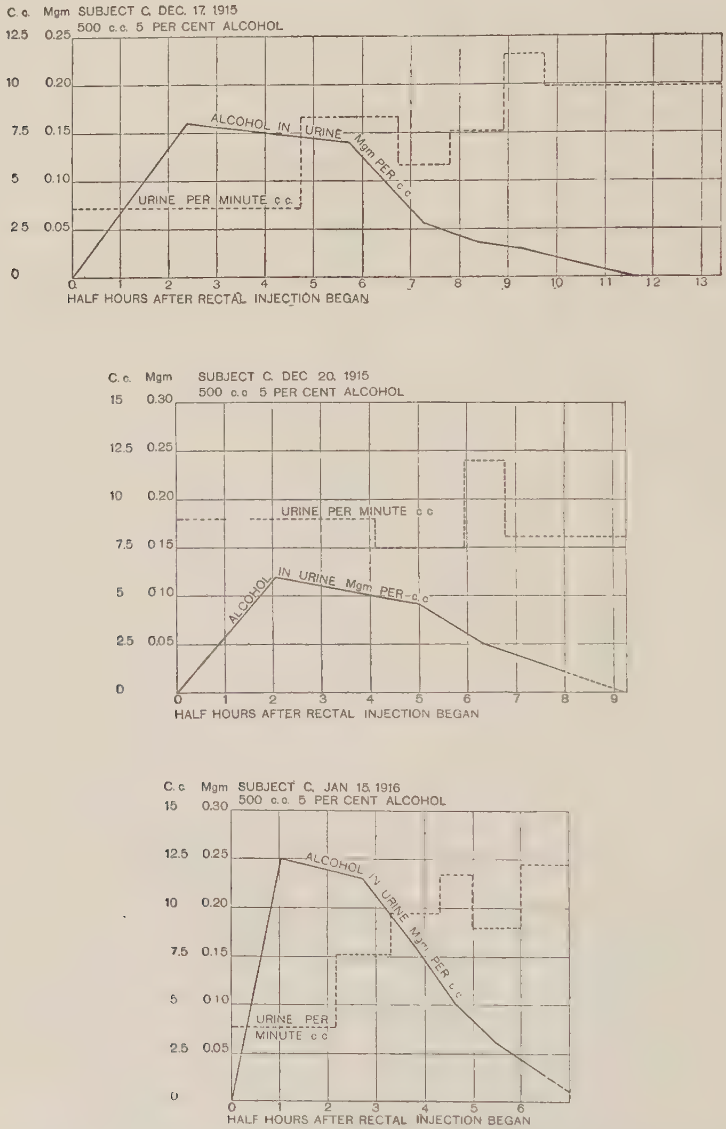


FIG. 2.—Milligrams of alcohol per cubic centimeter of urine, and volume of urine per minute, after rectal injection of 500 c. c. of a 5 per cent (by weight) alcohol solution.

No alcohol was found at $10^h$ $05^m$ p. m. (4 hours and 47 minutes after the injection began), and there was none obtained subsequently, except for a possible trace in the urine collected by the subject the following morning. The average concentration was 0.16 mg. per cubic centimeter, while the total alcohol eliminated in the urine was 316 mg., or 1.4 per cent of the total amount of alcohol injected.

The results of these experiments are also expressed graphically by means of charts. (See figs. 1 to 3.) In these curves the milligrams of alcohol per cubic centimeter of urine are plotted at the middle of the period *this point being*

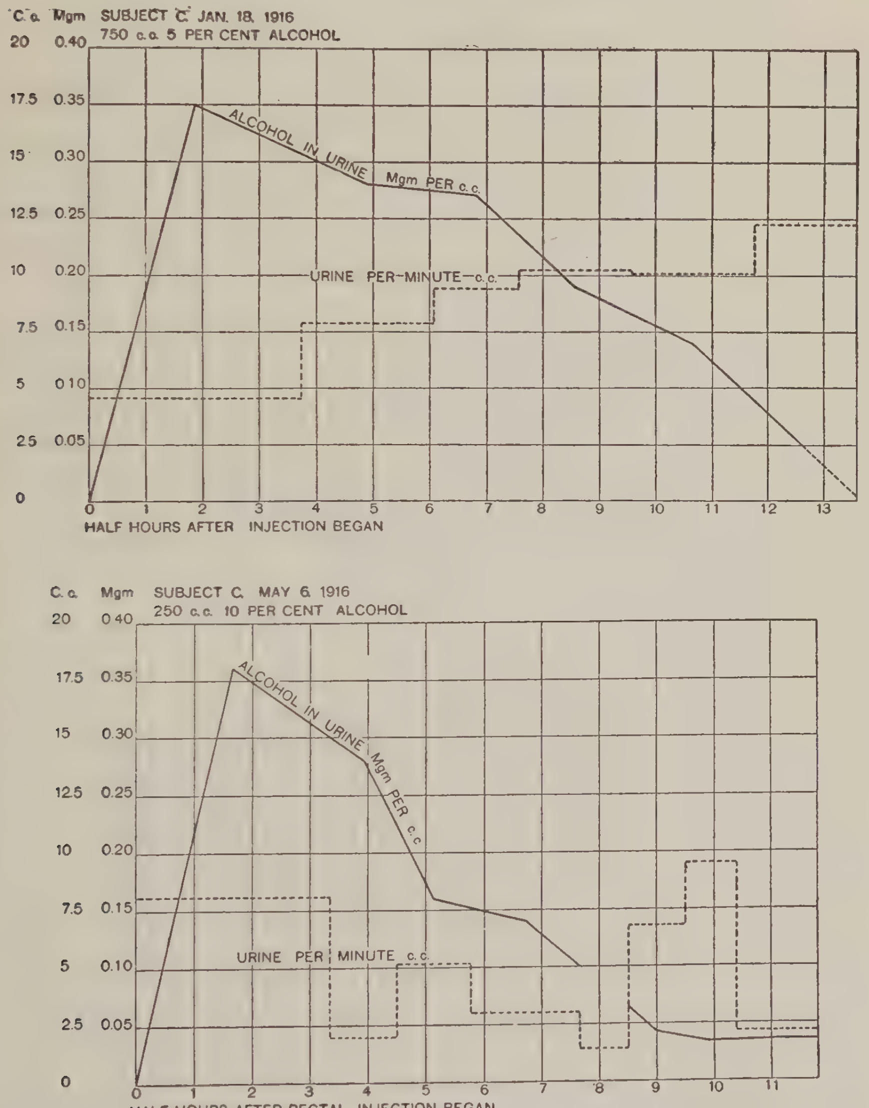


FIG. 3.—Milligrams of alcohol per cubic centimeter of urine, and volume of urine per minute, after rectal injection of 750 c. c. of a 5 per cent (by weight) alcohol solution, and 250 c. c. of a 10 per cent (by weight) a cohol solution.

*considered to give an average for that period, not a concentration at a single point of time.* The average volume per minute is plotted by the "block" method, that is, the horizontal line represents the whole period and the vertical lines indicate the ends of the periods. In presenting the results in the tables and charts, the experiments are arranged first, according to the percentage of alcohol in the solution, and second, according to the volumes of the alcohol solutions injected.

## COMPARISON EXPERIMENTS WITH URINE COLLECTED AT SHORT INTERVALS AFTER INGESTION OF ALCOHOL SOLUTIONS BY MOUTH.

In addition to these experiments with rectal injection, it was thought desirable to have comparison experiments in which the urine was likewise collected at short intervals, but the alcohol solution was given by mouth.[1] In the experiments here recorded the subjects passed urine, then immediately took the alcohol in water, drinking it as quickly as possible. The data for the experiments are given in table 13 and in figure 4, the method of presentation being the same as for the experiments in which the solutions were given rectally.

There were 4 experiments in all, 2 each with subjects A and C. In the first 3, 25 grams of alcohol were given by mouth in a 5 per cent alcohol solution, and in the final experiment the same amount was given in a 10 per cent solution. In all but one of the group the first collection of urine was earlier than in the rectal experiments, being but 45 or 27 minutes after the injection began, but the observations were not usually made over so long a period, and in but one case did the alcohol entirely disappear from the urine. As with the rectal experiments, the highest concentration was found in the first or second sample of urine, and always within 2 hours. The results of the rectal and mouth experiments will be compared in the general discussion of these short-period observations.

## DISCUSSION OF THE RESULTS OBTAINED WITH SHORT PERIODS OF URINE COLLECTION.

The collection of the urine in short periods after giving by rectum and by mouth alcohol solutions with concentrations of 5 and 10 per cent has brought out several features. In the first place, there was a very distinct peak, that is, a point of time at which the highest concentration was obtained. An examination of the several charts shows that this peak occurred in every instance within the first 2 hours, and in the first or second collection period. Unfortunately, in many of the rectal experiments, the first collection of urine did not follow so soon after the introduction of alcohol as might be desired, although theoretically it should be possible to obtain these collections in extremely short periods, as Widmark has done.[2] It is therefore quite likely that the actual peak sometimes occurred even earlier than was found.

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[1]A more intensive study of this character has since been carried out in this Laboratory by Miles, and published. (Miles: Journ. Pharm. and Exp. Therapeutics, 1922, 20, p. 265, *Ibid.*, Carnegie Inst. Wash. Pub. No. 333, 1924, pp. 211 to 222.)

[2] Widmark: Skand. Arch. f. Physiol., 1916, 33, p. 85.

TABLE 13.—*Elimination and concentration in urine of alcohol ingested by mouth.*

| Subject, date, and time of urinating. | Length of period. | Time since alcohol ingested. | Volume of urine. Total. | Volume of urine. Per min. | Alcohol excreted in urine. Total. | Alcohol excreted in urine. Per c. c. of urine. |
|---|---|---|---|---|---|---|
| C. Jan. 8, 1916: | *min.* | *h. min.* | *c. c.* | *c. c.* | *mg.* | *mg.* |
| $1^h$ $45^m$ p. m.[a] | 330 | .. .. | 227 | 0.7 | ... | .... |
| 1 50 to $1^h$ $53^m$ p. m. | 500 c. c. of 5 p. ct. solution. | | | | | |
| 2 35 p. m. | 50 | 0 45 | 42 | .8 | 13 | 0.31 |
| 3 18 | 43 | 1 28 | 310 | 7.2 | 83 | .27 |
| 3 54 | 36 | 2 4 | 355 | 9.9 | 74 | .21 |
| 4 35 | 41 | 2 45 | 412 | 10.0 | 73 | .18 |
| 5 18 | 43 | 3 28 | 463 | 10.8 | 43 | .09 |
| 5 58 | 40 | 4 8 | 542 | 13.6 | 24 | .05 |
| Total | ... | .. .. | ... | .... | [b]310 | .... |
| Average | ... | .. .. | ... | .... | ... | 0.15 |
| A. Jan. 8, 1916: | | | | | | |
| $1^h$ $45^m$ p. m.[a] | 705 | .. .. | 320 | 0.5 | ... | .... |
| 1 50 to $1^h$ $53^m$ p. m. | 500 c. c. of 5 p. ct. solution. | | | | | |
| 2 35 p. m. | 50 | 0 45 | 71 | 1.4 | 23 | 0.33 |
| 3 17 | 42 | 1 27 | 345 | 8.2 | 132 | .38 |
| 3 53 | 36 | 2 3 | 405 | 11.2 | 134 | .33 |
| 4 35 | 42 | 2 45 | 437 | 10.4 | 102 | .23 |
| 5 17 | 42 | 3 27 | 442 | 10.5 | 65 | .15 |
| 5 57 | 40 | 4 7 | 480 | 12.0 | 28 | .06 |
| Total | ... | .. .. | ... | .... | [b]484 | .... |
| Average | ... | .. .. | ... | .... | ... | 0.22 |
| A. Jan. 12, 1916: | | | | | | |
| $4^h$ $45^m$ p. m.[a] | 195 | .. .. | 90 | 0.5 | ... | .... |
| 4 50 | 500 c. c. of 5 p. ct. solution. | | | | | |
| 6 45 | 120 | 1 55 | 363 | 3.0 | 120 | 0.33 |
| 7 45 | 60 | 2 55 | 417 | 7.0 | 85 | .20 |
| 8 47 | 62 | 3 57 | 462 | 7.5 | 40 | .10 |
| 9 26 | 39 | 4 36 | 316 | 8.1 | 10 | .03 |
| 9 55 | 29 | 5 5 | 235 | 8.1 | Trace | .... |
| 10 32 | 37 | 5 42 | 245 | 6.6 | 0 | .... |
| Total | ... | .. .. | ... | .... | [b]255 | .... |
| Average | ... | .. .. | ... | .... | ... | 0.16 |
| C. Apr. 20, 1916: | | | | | | |
| $12^h$ $32^m$ p. m.[a] | 212 | .. .. | 149 | 0.7 | ... | .... |
| 12 33 to $12^h$ $36^m$ p. m. | 250 c. c. of 10 p. ct. solution. | | | | | |
| 1 00 p. m. | 28 | 0 27 | 44 | 1.6 | 7 | 0.16 |
| 1 35 | 35 | 1 2 | 295 | 8.4 | 113 | .38 |
| 2 13 | 38 | 1 40 | 250 | 6.6 | 74 | .30 |
| 2 50 | 37 | 2 17 | 295 | 8.0 | 58 | .20 |
| 3 43 | 53 | 3 10 | 200 | 3.8 | 31 | .15 |
| 4 25 | 42 | 3 52 | 136 | 3.2 | 10 | .08 |
| 5 20 | 55 | 4 47 | 289 | 5.3 | 14 | .05 |
| 5 52 | 32 | 5 19 | 228 | 7.1 | 7 | .03 |
| 6 28 | 36 | 5 55 | 220 | 6.1 | 6 | .03 |
| 6 55 | 27 | 6 22 | 73 | 2.7 | 2 | .03 |
| Total | ... | .. .. | ... | .... | [b]323 | .... |
| Average | ... | .. .. | ... | .... | ... | 0.15 |

[a] Urine passed before the experiment, but not saved, at the following times: C, Jan. 8, $8^h$ $15^m$ a. m.; A, Jan. 8, 7 a. m; Jan. 12, $1^h$ $30^m$ p. m.; Apr. 20, 9 a. m.

[b] The proportional part of the alcohol injected which was eliminated in the urine was as follows: C, Jan. 8, 1.2 p. ct.; A, Jan. 8, 1.9 p. ct.; Jan. 12, 1 p. ct.; Apr. 20, 1.3 p. ct.

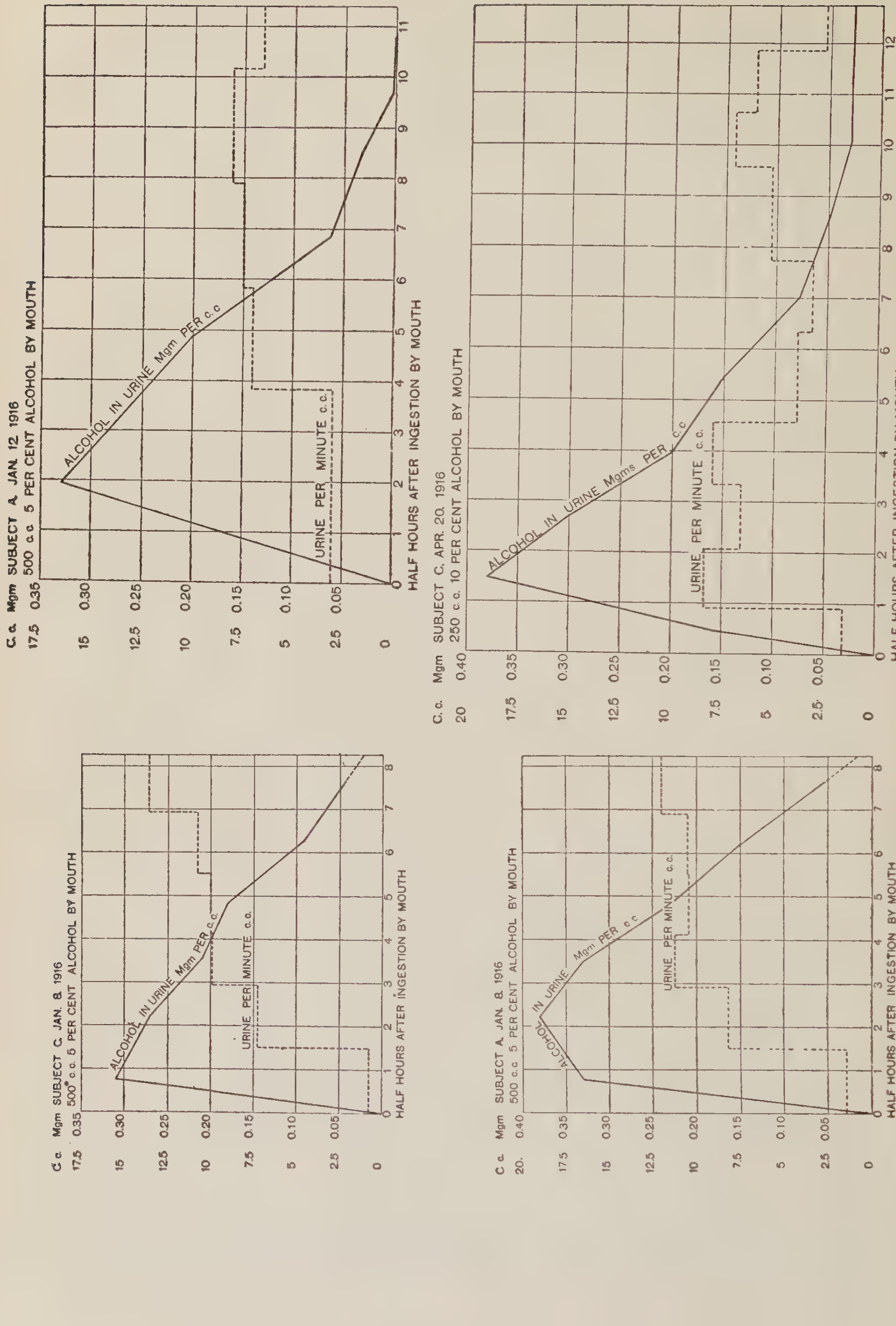


FIG. 4.—Milligrams of alcohol per cubic centimeter of urine, and volume of urine per minute after ingestion by mouth of 25 grams of alcohol in 5 per cent and 10 per cent (by weight) solutions.

There were several instances in the mouth experiments in which the first collection was made within an hour, and in nearly all of both groups of experiments the first alcohol urine was obtained within 2 hours. When the volume of alcohol introduced was below 500 c. c. of a 5 per cent solution (less than 25 grams by weight), the alcohol concentration of the urine collected in the second period was the same or higher than that of the first period, that is, the peak occurred in the second hour. (See fig. 1.) On the other hand, when the volume of the 5 per cent solution was 500 c. c. and over, or a 10 per cent solution was used, i. e., 25 or more grams of alcohol, the sample collected in the first period had the maximum concentration, the peak occurring in or near the first hour when the first collection was early enough to show the probable true maximum. This is also true of all the mouth experiments, except possibly that with A on January 8. In the mouth experiment on April 20, the first collection period was but 27 minutes long, and accordingly the maximum concentration did not occur until the second period, ending 1 hour and 2 minutes after the beginning of the injection.

The concentration of alcohol in the urine can be taken as an indication of the actual content of alcohol in the body, or rather of the changes in its concentration in the body. In the earlier part of the experiment, at least, the alcohol concentration in the urine must represent the balance between the absorption and the utilization of the amount injected, for if we have a curve in which successive samples of urine show higher concentrations of alcohol, we must believe that the absorption is taking place more rapidly than the utilization or disappearance. Since with an injection of 25 grams of alcohol or over, the urine collected in the first hour had the maximum concentration, it is apparent that the higher the alcohol-content of the solution, the more quickly is the peak of concentration in the body reached. In other words, the time the peak occurs is dependent upon the amount of alcohol introduced. A comparison of the two rectal experiments of January 18 and May 6, with the same subject and with the length of the first collection period approximately the same, indicates that the concentration of the alcohol in the solution injected may also have a bearing upon the time of maximum concentration in the urine eliminated, for although in the experiment with the 10 per cent solution but 25 grams of alcohol were injected, as compared with 37.5 grams in the experiment with the 5 per cent solution, the concentration in the urine reached the peak at apparently about the same time as indicated by the amount of concentration.

The time of disappearance of alcohol from the urine after the occurrence of the peak was not determined in all cases, as the observations were not always of sufficient length. In the first 5 experiments with rectal injection, the last urine collections contained no alcohol; consequently these observations were continued to a point when the alcohol elimination had ceased. With possibly one exception (the experiment of December 17 with C), the time covered by the total alcohol elimination in these 5 experiments was under 5 hours. The conclusion may therefore be drawn that 25 grams of alcohol taken in the form of a 5 per cent solution, introduced rectally, disappears completely from the urine, and therefore presumably from the blood, within 5 hours. The experiments of December 20 and January 15 may also be considered as confirming this conclusion, for although the observations in short periods were not continued for a full 5 hours, yet the alcohol in the urine in the last observation in each experiment was near the vanishing-point.

The falling off in the concentration was less rapid than the rise in the beginning of the experiment, for as the absorption was ended and apparently a large amount of the alcohol had already been burned or utilized, there was less alcohol to burn, even at the peak of absorption, and consequently it disappeared at a slower rate.

In the experiment in which 750 c. c. of a 5 per cent alcohol solution were given (January 18), the time of disappearance of alcohol from the urine was somewhat later than in the earlier experiments, in which the volume of the solution and amount of alcohol were less. Notwithstanding the fact that the experiment on January 18 was continued for nearly 7 hours after the injection, the alcohol did not completely disappear from the urine. In the experiment in which 250 c. c. of a 10 per cent solution were given (May 6), with a smaller content of alcohol than in the preceding experiment, the result was apparently of the same order as with 750 c. c. of the 5 per cent solution, for at the end of 6 hours there was still a recognizable amount of alcohol in the urine.

The actual concentration of alcohol in the urine in the 9 rectal experiments varied from 0.02 mg. to 0.36 mg. per cubic centimeter of urine. The last value was obtained in the experiment with 250 c. c. of a 10 per cent solution, but nearly the same concentration (0.35 mg.) was obtained in the experiment with 750 c. c. of a 5 per cent alcohol solution, i. e., 37.5 grams of alcohol.

There was a slight tendency for the higher amounts of alcohol to give a higher absolute maximum, but the body-weight of the two subjects must be taken into consideration in determining this point. The body-weight of C was about 70 kg., while that of A was 54 kg. Accordingly, we would expect that with the same amount of alcohol, the concentration with subject C would be lower than that with subject A. This was apparently true, for subject C with 470 c. c. of a 5 per cent solution had a maximum concentration of 0.18 mg., while subject A, with the some amount of alcohol, had a maximum of 0.27 mg. Unfortunately, all of the remaining observations were with subject C, with whom there was a variation in the maxima, for in experiments with 500 c. c. of a 5 per cent solution, they ranged from 0.12 to 0.25. In the last two experiments with C, the amounts of alcohol given were 37.5 grams and 25 grams, the first in a 5 per cent solution, and the second in a 10 per cent solution. In each of these experiments the maxima were somewhat higher, namely, 0.35 and 0.36 mg.

The experiments in which the alcohol was introduced by mouth may also be discussed. The collection of urine was not so complicated in these experiments as in those with rectal injection, and in 3 out of 4 instances a fairly early collection of urine was obtained—from 27 to 45 minutes after the alcohol was taken. The time of occurrence of the maximum or peak of the concentration of alcohol in the urine has already been discussed in the consideration of the rectal experiments in this series. (See p. 55.) While it is somewhat difficult to compare the two groups of rectal and mouth experiments as to the time the peak occurred, apparently when the alcohol was directly introduced by mouth the maximal concentration was obtained but little before that in the experiments when the alcohol was introduced rectally, certainly not more than one-half hour earlier.

The maximal concentration of alcohol in the urine in the 4 mouth experi-

ments ranged between 0.38 mg. and 0.31 mg. per cubic centimeter of urine, the average maxima being materially higher than those in the experiments with alcohol introduced by rectum, even when we compare the experiments in which the amount and concentration in solution were the same, i. e., 25 grams in a 5 per cent solution. In all probability, the higher maxima in the mouth experiments were not due to the delayed collection of the urines in the rectal experiments, but either to a more rapid absorption, that is, the alcohol reached the blood more quickly, or to a slower utilization of the alcohol when it was introduced by mouth, so that the maximal concentration in the urine rose to a higher point than with rectal injection. Owing to the length of the absorption experiments (2 to 6 hours), we have no measure of the rate of absorption of this quantity of alcohol introduced by rectum except in one comparatively short experiment, in which it was found that, after 1 hour, nearly all of the alcohol had been absorbed. (See experiment with A, April 10, table 3, p. 29.) From this one experiment it would appear that the absorption of alcohol introduced rectally is very rapid, and presumably almost as rapid as when alcohol is introduced by mouth.

The time that the alcohol disappeared from the urine was ascertained in only one of the mouth experiments, that with subject A, January 12, and on this date it was at the end of 5 hours. (See table 13.) It would appear from the shape of the concentration curves for the 4 mouth experiments with alcohol (fig. 4) that it did not disappear quite so rapidly from the body or, more accurately, from the urine itself, as when introduced rectally. This would lead to the conclusion that the rapidity of utilization or disappearance of alcohol from the urine is not so great when it is ingested by mouth as when the introduction is rectal. It must be admitted that the number and completeness of the experiments are not sufficient to warrant the drawing of this conclusion without some reserve, but the data are fairly consistent and should be taken into consideration in comparing the effect of alcohol when introduced into the body by these two methods. This phase of the problem will be fully discussed in connection with the respiratory exchange and heart-rate. (See p.139.)

In these experiments with ingestion by mouth, we also have a confirmation of the statement of Widmark [1] and of Miles [2] to the effect that the diuresis has no effect upon the actual concentration. In other words, in spite of the greater quantity of urine eliminated in the later periods of the experiments, there is no parallelism between the dilution of urine and the alcohol concentration. At first glance it would seem as if there were such a connection, because in many experiments the curve for the urine elimination per minute and that for the concentration per cubic centimeter of urine are reciprocal, but there is no regularity about this relationship, as there are a number of experiments in which the amount of urine eliminated per minute does not vary from period to period, while the concentration curve shows a sharp upward movement and a more gradual descent.

The percentage of the total amount of alcohol introduced which was eliminated in the urine varied in the mouth experiments from 1.0 to 1.9. In general the percentages were significantly higher than those in experi-

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[1] Widmark: Skand. Arch. f. Physiol., 1916, 33, p. 85.

[2] Miles: Journ. Pharm. and Exp. Therapeutics, 1922, 20, p. 265; *Ibid.*, Carnegie Inst. Wash. Pub. No. 333, 1924, p. 138.

ments previously discussed (see tables 8, 9, 10, and 11), in which only one or two collections of urine were made. This was due to the larger amount of urine eliminated. Other things being equal, the larger the amount of urine eliminated after the taking of alcohol, the greater will be the percentage of elimination of alcohol. However, unlimited drinking of water or other liquid would be required to produce a significant effect upon the elimination of alcohol in the urine and its disappearance from the system. The fact must be noted, also, that in the earlier series the periods of observations were not sufficiently extended to insure the total collection of the alcohol eliminated, since they did not reach a point when alcohol was absent from the urine. These two groups of experiments were not sufficiently extensive to bring out any difference in the two individuals as to the rate of disappearance of the alcohol.

Observations are needed to ascertain whether this method would be satisfactory for a comparison of subjects who absorb alcohol rapidly with those who lack so great a power of utilization.

## EFFECT OF COFFEE DRINKING ON ELIMINATION OF A REDUCING SUBSTANCE.

On December 20, subject C drank clear coffee before the alcohol was injected in order to promote a freer flow of urine, i. e., diuresis. A collection of urine was made at $6^h\ 10^m$ p. m. and a determination of alcohol (i. e., potassium-bichromate reduction) was made; the amount of bichromate reduced corresponded to 25 mg. of alcohol. A similar determination was made for a sample collected at $6^h\ 25^m$ p. m., which showed no reducing power for the potassium bichromate. It has since been substantiated that the ingestion of coffee extract will result in a urinary excretion of a substance capable of reducing potassium bichromate.

## CONJUGATED ALCOHOL.

The occurrence of alcohol in the urine in a conjugated state has been reported by Neubauer [1] in an extensive investigation with compounds of the fatty-acid series upon the pairing of substances with glucuronic acid and elimination in the urine. He gave ethyl alcohol to 2 rabbits and 2 dogs and proved the occurrence of glucuronic acid in the urine by polarization and by difference in reduction before and after hydrolysis. In one case he distilled the urine after hydrolysis and found the iodoform test to be positive and also determined the presence of acetaldehyde after heating with potassium bichromate and sulphuric acid. The urine of the two rabbits gave relatively the same amount of levo-rotation, but with one dog the evidence was indecisive, while with the other it was positive. He reports no values for the quantity of alcohol eliminated in this manner.

In the series of determinations of alcohol in urine included in the present research with human subjects, the urine was distilled in a large number of cases without the addition of a hydrolyzing agent, while to other portions of the same urine was added 1 c. c. of concentrated hydrochloric acid, and they were then distilled. In several cases, 5 c. c. of 85 per cent phosphoric acid

[1] Neubauer: Arch. f. exp. Path. u. Pharm., 1901, 46, pp. 135–142.

were added to the 1 c. c. of concentrated hydrochloric acid. The great majority of the determinations showed no difference in the titration figures between the distillation from the untreated urine and the distillation from that treated with the acid. There were, however, several cases in which the treatment with the inorganic acid gave a higher titration.

In the previous tables the total alcohol in the urine as recorded was obtained by distillation with inorganic acids, on the basis that the additional material which was distilled was alcohol. In the experiment with subject A on November 18, the free alcohol in the urine was 85 mg., while the conjugated alcohol, plus the free alcohol, was 108 mg. (See table 8, p. 39.) Thus there were 23 mg. in the urine which were in the conjugated state. With subject D, March 3, 1916, the titration without hydrochloric acid of the urine obtained in the second collection gave 26 mg., and with hydrochloric acid gave 37 mg., with a difference of 11 mg. of conjugated alcohol. (See table 9, p. 41.) With subject A, on March 27, 1916, the free alcohol was 99 mg., while the total alcohol was 129 mg.; thus the conjugated alcohol was 30 mg. With subject C, on April 1, there were 79 mg. of free alcohol and 104 mg. of total alcohol, or 25 mg. of conjugated alcohol. (See table 11, p. 44.)

No efforts were made at that time to investigate the character of the conjugation, but presumably it was with glucuronic acid as found by Neubauer. The conjugation of alcohol is of interest, as it suggests the possibility of a difference in the way alcohol may be metabolized, that is, it may be coupled with another substance and then subsequently oxidized.

Further studies would be of value in which a glucoside of alcohol, such as a combination of glucose and alcohol, should be given and the respiratory exchange and the alcoholic content of urine studied to see if, with this molecular ratio, there would be a change in the character of the metabolism and in the rate at which alcohol appeared in the blood and urine. Additional experiments might be made to determine whether different results would be obtained with different methods of introduction, i. e., by mouth or by rectum, in order to ascertain whether the coupling is carried out through the liver itself or whether it is carried out when the liver is actively engaged in forming materials with a possible secretion of a hormone distributed throughout the body. In the latter case it is not meant that the transformation takes place actually in the liver, but when the liver is actively engaged in metabolic transformation. These suggested experiments show the great value of using ethyl alcohol in rectal studies of humans from the standpoint of pure physiology.

## EFFECT OF RECTAL INJECTIONS UPON VOLUME OF URINE AND ELIMINATION OF NITROGEN AND SODIUM CHLORIDE.

In addition to the studies of the elimination and the concentration in the urine of alcohol given both by rectal injection and by mouth, observations were made of the volume of urine and the nitrogen and sodium-chloride contents with rectal injection. These records were obtained not only for the experiments in which alcohol injections were given, but in like experiments with solutions of sodium chloride, dextrose, and levulose. As previously noted (p. 23), the alcohol was diluted with distilled water, whereas the

levulose, and usually the dextrose, were given in a 0.6 per cent solution of sodium chloride.

The results are gathered together into tables, with records for the individual experiments of the dates, subjects, volumes of solution, and weights of the specific materials in the solutions. The urine data are divided into two groups. The first group represents the so-called preliminary period and the results were obtained by analyzing the urines from the first urination, which immediately preceded the experimental observations. These urines were therefore secreted during the time between the last urination previous to the coming of the subject to the Laboratory and that of the first urination before the experiment. It must be borne in mind that the length of this preliminary period is somewhat uncertain in that the accuracy of the time of the previous urination depends wholly upon the subject's memory. Undoubtedly there is some error in these records, but as this affects all the groups of experiments, the possible inaccuracy is disregarded, since the chief object is to find whether there are any characteristic features of the groups as a whole in respect to volume, nitrogen, and sodium chloride.

The second group of data represents the urines collected between the first and last urinations while the subject was under observation. The length of this period of secretion is accurate, as the time records were made by the observer. The data include, however, not only the urine secreted after the injection of the solution, but also that secreted from the time of the first urination of the subject at the Laboratory to the giving of the injection. These results therefore represent a mixture of the normal urine and of urine secreted after injection, as was the case with the urines for the long periods of collection in the discussion of elimination and concentration in the preceding section. (See p. 38.) In both groups records are made of the lengths of the periods of secretion, the per hour values for the volumes of urine, the nitrogen and the sodium-chloride contents, and the ratios between these two substances. The records for the experimental urines also include statements as to the periods of time after the injection which are included in the whole periods of secretion. The ratio between the nitrogen and sodium chloride has no particular physiological significance, but is simply a mathematical expression for determining the change in the relationship after the injection of the solution, this indicating the difference between the two factors in the change in rate of elimination.

The results obtained for injections of sodium-chloride solution are first discussed, and subsequently those for alcohol injections in the several concentrations, and finally those for sugar solutions.

## Effect on Urine of Rectal Introduction of a Solution of Sodium Chloride.

In table 14 the statistics are presented for 13 experiments in which 0.6 per cent solutions of sodium chloride were given and urines were voided and collected both for the preliminary period and for the experimental period before and after the solution was injected. The volumes of the solution introduced rectally varied from 220 c. c. to 520 c. c., while the sodium chloride in the injection ranged between 1.3 and 3.1 grams.

The length of the preliminary period averaged 239 minutes, with a range between 120 and 485 minutes, the latter case being the long experiment in

TABLE 14.—*Effect upon volume of urine and elimination of nitrogen and of sodium chloride of a sodium-chloride solution introduced by rectum. (Values per hour.)*

| Date. | Subject. | Solution injected. | | Preliminary urine (before solution given). | | | | | Experimental urine (before and after solution given). | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Volume. | Weight of sodium chloride. | Length of period. | Volume. | Nitrogen. | NaCl. | Ratio $\frac{N}{NaCl}$ | Length of experimental period. | Portion of period after salt injected. | Volume. | Nitrogen. | NaCl. | Ratio $\frac{N}{NaCl}$ |
| | | *c. c.* | *grams.* | *min.* | *c. c.* | *mg.* | *mg.* | | *min.* | *min.* | *c. c.* | *mg.* | *mg.* | |
| 1915 Oct. 7 | B | 220 | 1.3 | 322 | 37 | 474 | 451 | 1.05 | 273 | 164 | 99 | 564 | 429 | 1.32 |
| 1916 Mar. 14 | A | 260 | 1.6 | 210 | 31 | 429 | 447 | .96 | 305 | 179 | 80 | 409 | 273 | 1.50 |
| Mar. 20 | A | 260 | 1.6 | 195 | 39 | 221 | 628 | .35 | 260 | 113 | 69 | 514 | 584 | .88 |
| 1915 Oct. 21 | B | 320 | 1.9 | 460 | 36 | 409 | 201 | 2.04 | 205 | 37 | 35 | 491 | 483 | 1.02 |
| Oct. 21 | C | 320 | 1.9 | 165 | 189 | 529 | 1659 | .32 | 275 | 135 | 214 | 453 | 772 | .59 |
| Oct. 19 | A | 325 | 2.0 | 139 | 25 | 424 | 390 | 1.09 | 301 | 179 | 13 | 302 | 130 | 2.39 |
| Nov. 21 | A | 400 | 2.4 | 245 | 50 | 736 | 490 | 1.50 | 280 | 165 | 104 | 625 | 740 | .84 |
| Nov. 4 | A | 420 | 2.5 | 120 | 55 | 371 | 630 | .60 | 305 | 165 | 34 | 304 | 80 | 3.80 |
| Nov. 2 | C | 420 | 2.5 | 170 | 158 | 536 | 1670 | .32 | 305 | 178 | 118 | 416 | 606 | .69 |
| Dec. 20 | A | 500 | 3.0 | 160 | 42 | 510 | 524 | .97 | 320 | 142 | 81 | 356 | 54 | 6.60 |
| Dec. 8 | A | 520 | 3.1 | 185 | 31 | 387 | 500 | .77 | 325 | 220 | 43 | 384 | 107 | 3.59 |
| Feb. 21 | C | 520 | 3.1 | 255 | 45 | 541 | 662 | .82 | 280 | 132 | 104 | 572 | 289 | 1.98 |
| 1917 Feb. 9 | A | 500 | 3.0 | 485 | 43 | 474 | 771 | .62 | 615 | 385 | 47 | 387 | 260 | 1.49 |
| Average | | ... | ... | 239 | 60 | 465 | 694 | .88 | 311 | 169 | 80 | 444 | 370 | 2.05 |

1917. The volume of urine per hour in the preliminary period was on the average 60 c. c. and varied from 25 to 189 c. c. The nitrogen per hour averaged 465 mg., with a range of 221 to 736 mg. The average sodium chloride was 694 mg., with a variation from 201 to 1,670 mg. The average ratio of nitrogen to sodium chloride was 0.88, with a range from 0.32 to 2.04.

The duration of the whole experimental period averaged 311 minutes, the individual experiments ranging in length between 205 and 615 minutes. This period of secretion was therefore somewhat longer than the period before the experiment. Of this 311 minutes, an average of 169 minutes represented the portion of time after the injection of the solution first began. This part of the period varied from 113 to 385 minutes, except in one experiment, when it was but 37 minutes. In general, therefore, over one-half of the collection for the experimental period represented urine which was secreted after the solution had been given. The volume of urine per hour ranged from 13 c. c. to 214 c. c., with an average of 80 c. c. This average is slightly higher than that for the preliminary period, but apparently this has little significance in showing that the volume was greater in the experimental period, for in a number of instances it was distinctly lower than that of the preliminary secretion. The nitrogen per hour averaged 444 mg., this being slightly lower than in the preliminary period, and ranged from 302 to 625 mg. The sodium chloride was 370 mg. per hour, or somewhat more than one-half that for the preliminary period, and ranged from 54 to 772 mg. The nitrogen-sodium chloride ratio was 2.05 on the average, thus indicating that, relatively, the change in the elimination of sodium chloride was greater than the change in the elimination of nitrogen.

The figures on the whole are regular enough for purposes of comparison with other groups. There are, however, some extreme values. For example, in the nitrogen data for the preliminary period, that for the experiment with A on November 21 was 736 mg., but the corresponding one for the experimental period was likewise high. The sodium-chloride values in the preliminary periods for C on October 21 and on November 2 are distinctly high. The discussion of the total effects of the injection of the solution of sodium chloride is reserved until all the other material has been presented and will be considered in connection with the percentile changes.

### Effect on Urine of Rectal Introduction of a 5 per cent Solution of Alcohol.

There were 14 experiments, in which a 5 per cent alcohol solution was given rectally and the urine collected both before the experiment began and during the experiment itself. The data are given in table 15. The volume of the injection varied from 300 c. c. to 520 c. c., and the amount of alcohol in these quantities from 15 to 26 grams.

The average length of the period before the experiment began was 226 minutes, with variations from 85 to 700 minutes. Many of the periods are under 200 minutes, the average being raised by the long period with B on October 31, which really included the urine for the night preceding the experiment. The volume per hour averaged 53 c. c., and varied from 26 to 81 c. c. The average nitrogen per hour was 460 mg., with individual values from the low figure of 277 mg. with B on October 31, to 694 mg. with the same subject on October 17. The sodium chloride per hour was 574 mg., with a

TABLE 15.—*Effect upon volume of urine and elimination of nitrogen and of sodium chloride of a 5 per cent alcohol solution introduced by rectum. (Values per hour.)*

| Date. | Subject. | Alcohol injected. | | Preliminary urine (before alcohol given). | | | | | Experimental urine (before and after alcohol given). | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Volume of solution. | Weight of alcohol. | Length of period. | Volume. | Nitrogen. | NaCl. | Ratio $\frac{N}{NaCl}$ | Length of experimental period. | Portion of period after alcohol injected. | Volume. | Nitrogen. | NaCl. | Ratio $\frac{N}{NaCl}$ |
| 1915 | | *c. c.* | *grams.* | *min.* | *c. c.* | *mg.* | *mg.* | | *min.* | *min.* | *c. c.* | *mg.* | *mg.* | |
| Oct. 17 | B | 300 | 15 | 362 | 77 | 694 | 388 | 1.79 | 351 | 257 | 72 | 465 | 614 | 0.76 |
| Oct. 31 | B | 320 | 16 | 700 | 63 | 277 | 199 | 1.39 | 275 | 214 | 89 | 452 | 570 | .79 |
| Oct. 29 | C | 320 | 16 | 145 | 42 | 390 | 770 | .51 | 290 | 231 | 112 | 335 | 336 | 1.00 |
| Nov. 8 | C | 320 | 16 | 165 | 36 | 507 | 550 | .92 | 315 | 210 | 28 | 395 | 165 | 2.40 |
| Nov. 14 | C | 320 | 16 | 90 | 65 | 553 | 1006 | .55 | 285 | 183 | 236 | 540 | 964 | .56 |
| Oct. 24 | C | 325 | 16.3 | 85 | 63 | 598 | 266 | 2.25 | 285 | 166 | 189 | 512 | 373 | 1.37 |
| Nov. 16 | B | 335 | 16.8 | 205 | 48 | 497 | 345 | 1.44 | 205 | 76 | 212 | 598 | 302 | 1.98 |
| Nov. 18 | A | 400 | 20 | 235 | 81 | 406 | 905 | .45 | 245 | 127 | 144 | 320 | 145 | 2.21 |
| Nov. 24 | A | 420 | 21 | 175 | 70 | 416 | 900 | .46 | 295 | 170 | 129 | 317 | 125 | 2.54 |
| Dec. 2 | A | 420 | 21 | 225 | 43 | 490 | 664 | .74 | 325 | 206 | 89 | 451 | 334 | 1.35 |
| Nov. 29 | C | 420 | 21 | 165 | 26 | 451 | 380 | 1.18 | 270 | 160 | 34 | 394 | 162 | 2.43 |
| 1916 | | | | | | | | | | | | | | |
| Apr. 3 | A | 510 | 25.5 | 280 | 29 | 435 | 443 | .98 | 305 | 255 | 149 | 429 | 124 | 3.46 |
| Feb. 25 | D | 510 | 25.5 | 205 | 56 | 360 | 746 | .48 | 300 | 197 | 202 | 361 | 223 | 1.62 |
| Feb. 18 | D | 520 | 26 | 130 | 40 | 360 | 474 | .76 | 320 | 218 | 133 | 381 | 160 | 2.38 |
| Average | | ... | .... | 226 | 53 | 460 | 574 | .99 | 290 | 191 | 130 | 425 | 328 | 1.77 |

variation of from 199 mg. to 1,006 mg. The ratio of nitrogen to sodium chloride was on the average 0.99.

The length of the experimental period averaged 290 minutes. This was not materially different from the corresponding average in the sodium-chloride experiments, and a like similarity may be observed in the preliminary periods for the two groups of observations. The length of time after the injection began averaged 191 minutes. The volume of urine per hour was 130 c. c. on the average, somewhat more than double that during the preliminary period, that is, a diuresis. A positive increase was found in most of the experiments, so that this change represents an actual increase in volume of urine eliminated after the experiment began. The average nitrogen per hour was 425 mg., a slightly lower figure than that for the preliminary period. The sodium chloride per hour was very decidedly lower, i. e., 328 mg. per hour as compared with 574 mg. for the preliminary period. The change in these two quantities is reflected in the average ratio of nitrogen to sodium chloride, which is 1.77 in the experimental period as compared with 0.99 in the preliminary period.

### Effect on Urine of Rectal Introduction of a 7.5 per cent Solution of Alcohol.

In 10 experiments a 7.5 per cent solution of alcohol was introduced rectally and the urine collected before and after the experiment. The data for the volume of urine and elimination of nitrogen and sodium chloride are given in table 16. Five of these experiments, made in 1916, are averaged separately, as they differed from the rest of the group in that the experimental periods were somewhat shorter than in the 5 experiments conducted in 1917. In fact, the 1917 experiments were night experiments and the length of time which the urine collection covered was therefore somewhat greater.

In the first group the volumes of alcohol solution injected ranged from 265 to 510 c. c., with the amount of alcohol varying from 19.9 to 37.5 grams. The average length of the urine period preceding the experiment was 179 minutes. The average volume of urine per hour was 50 c. c., the nitrogen per hour 511 mg., the sodium chloride per hour 580 mg., and the ratio of nitrogen to sodium chloride 0.93. For purposes of comparison these values are sufficiently close in order of magnitude to those obtained in the preliminary periods of the experiments with a 5 per cent solution of alcohol.

The experimental urine periods in 1916 averaged 321 minutes in length, with the portion of time after the rectal injection 246 minutes. This is slightly longer than the period after injection with the preceding groups. The volume of urine averaged 135 c. c. per hour as compared with the much smaller average volume of 50 c. c. in the preliminary period. The nitrogen per hour was 442 mg., somewhat lower than that in the first urine collection. The sodium-chloride excretion was 287 mg. per hour. The ratio of nitrogen to sodium chloride was 1.75, showing a distinctly greater change in the output of sodium chloride than in the nitrogen.

In the 5 experiments conducted in 1917, all with the same subject, 37.5 grams of alcohol were given in 500 c. c. of a 7.5 per cent solution. The preliminary period averaged 160 minutes in length, which is comparable with the average for the first group. The volume per hour was 42 c. c., and likewise comparable with the 1916 group. The average nitrogen per hour

TABLE 16.—*Effect upon volume of urine and elimination of nitrogen and sodium chloride of a 7.5 per cent alcohol solution introduced by rectum. (Values per hour.)*

| Date. | Subject. | Alcohol injected. | | Preliminary urine (before alcohol given). | | | | | Experimental urine (before and after alcohol given). | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Volume of solution. | Weight of alcohol. | Length of period. | Volume. | Nitrogen. | NaCl. | Ratio N/NaCl | Length of experimental period. | Portion of period after alcohol injected. | Volume. | Nitrogen. | NaCl. | Ratio N/NaCl |
| 1916. | | *c. c.* | *grams.* | *min.* | *c. c.* | *mg.* | *mg.* | | *min.* | *min.* | *c. c.* | *mg.* | *mg.* | |
| Mar. 1 | C | 265 | 19.9 | 240 | 39 | 403 | 593 | 0.68 | 270 | 190 | 141 | 438 | 461 | 0.95 |
| Mar. 3 | D | 265 | 19.9 | 120 | 56 | 503 | 684 | .74 | 345 | 244 | 148 | 471 | 370 | 1.27 |
| Apr. 10 | A | 350 | 26.3 | 220 | 27 | 322 | 426 | .76 | 375 | 299 | 106 | 357 | 201 | 1.78 |
| Mar. 22 | C | 415 | 31.1 | 180 | 74 | 670 | 792 | .85 | 285 | 195 | 123 | 404 | 213 | 1.90 |
| Mar. 29 | C | 510 | 37.5 | 135 | 55 | 658 | 405 | 1.62 | 330 | 300 | 155 | 539 | 190 | 2.84 |
| Average | | ... | ... | 179 | 50 | 511 | 580 | 0.93 | 321 | 246 | 135 | 442 | 287 | 1.75 |
| 1917. | | | | | | | | | | | | | | |
| Jan. 20 | A | 500 | 37.5 | 265 | 35 | 451 | 637 | .71 | 600 | 421 | 58 | 343 | 65 | 5.28 |
| Feb. 3 | A | 500 | 37.5 | 175 | 45 | 304 | 883 | .35 | 680 | 465 | 67 | 344 | 278 | 1.24 |
| Feb. 15 | A | 500 | 37.5 | 100 | 41 | 435 | 807 | .54 | 715 | 483 | 58 | 310 | 144 | 2.15 |
| Mar. 2 | A | 500 | 37.5 | 165 | 44 | 812 | 532 | 1.53 | 688 | 573 | 68 | 637 | 110 | 5.79 |
| Mar. 23 | A | 500 | 37.5 | 95 | 44 | 654 | 630 | 1.04 | 695 | 449 | 55 | 423 | 93 | 4.55 |
| Average | | ... | ... | 160 | 42 | 531 | 698 | 0.83 | 676 | 478 | 61 | 411 | 138 | 3.80 |

was 531 mg., the sodium chloride 698 mg., and the ratio of nitrogen to sodium chloride 0.83. The experimental period was much longer than in the 1916 group, namely, 676 minutes on the average, and the time after the rectal injection began was 478 minutes. The volume per hour was 61 c. c., or slightly greater than in the preliminary period. The average nitrogen elimination per hour was 411 mg., about 25 per cent lower than the nitrogen output in the preliminary period. The sodium chloride likewise fell very materially, averaging 138 mg. per hour. This change is reflected in the much higher ratio of nitrogen to sodium chloride in the experimental period, namely, 3.80.

### Effect on Urine of Rectal Introduction of a 10 per cent Solution of Alcohol.

In 4 experiments 26 to 26.5 grams of alcohol were given in a 10 per cent solution, that is, in a volume of about 265 c. c. (See table 17.) The length of the preliminary period averaged 135 minutes, the average volume per hour was 64 c. c., while the average nitrogen elimination per hour was 478 mg. and the sodium chloride per hour 772 mg. The ratio of nitrogen to sodium chloride was 0.75. The quantities are therefore fairly comparable with those obtained in the preliminary periods of preceding groups.

The length of the experimental periods averaged 301 minutes, which corresponds generally with the preceding groups, except in the case of the 1917 experiments with a 7.5 per cent solution of alcohol. The portion of the period after the rectal injection began was 205 minutes. The average volume per hour was 133 c. c., twice that in the preliminary period. The average nitrogen excretion per hour was 374 mg., or a material fall on the average from the excretion found in the preliminary period. The sodium-chloride output per hour fell very considerably, the average being 295 mg. This decrease was reflected in the ratio of nitrogen to sodium chloride, which was 1.66 as compared with 0.75 in the preliminary period.

### Effect on Urine of Rectal Introduction of a Dextrose Solution.

In 9 experiments 30 grams of dextrose were introduced by rectum in 500 to 520 c. c. of a 0.6 per cent solution of sodium chloride, except on May 6 and 16, when a 5 per cent solution of alcohol was substituted for the sodium-chloride solution. The results are given in table 18. The average length of the preliminary period before the experiment began was 266 minutes, while the average volume of urine was 68 c. c. The nitrogen elimination per hour averaged 502 mg. and that of sodium chloride 595 mg.; the general ratio between the two was 0.92.

The collection period for the experimental urine, i. e., that secreted before and after the rectal injection began, averaged 363 minutes in length, and of this the observations made after the rectal injection commenced extended over 273 minutes. The volume of urine was 76 c. c. per hour, or a little more than that for the preliminary period. The nitrogen excretion was 415 mg. per hour, approximately 20 per cent lower than that for the preliminary period. The sodium-chloride output was 469 mg. per hour, or lower than in the preliminary period. The ratio of nitrogen to sodium chloride of 1.14 was only slightly higher than the ratio for the preliminary period, thus indicating that the changes in the elimination of both the nitrogen and the sodium chloride were more or less parallel.

TABLE 17.—*Effect upon volume of urine and elimination of nitrogen and sodium chloride of a 10 per cent alcohol solution introduced by rectum. (Values per hour.)*

| Date. | Subject. | Alcohol injected. | | Preliminary urine (before alcohol given). | | | | | Experimental urine (before and after alcohol given). | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Volume of solution. | Weight of alcohol. | Length of period. | Volume. | Nitrogen. | NaCl. | Ratio $\frac{N}{NaCl}$ | Length of experimental period. | Portion of period after alcohol injected. | Volume. | Nitrogen. | NaCl. | Ratio $\frac{N}{NaCl}$ |
| 1916 | | *c. c.* | *grams* | *min.* | *c. c.* | *mg.* | *mg.* | | *min.* | *min.* | *c. c.* | *mg.* | *mg.* | |
| Mar. 24......... | A | 260 | 26.0 | 70 | 17 | 311 | 229 | 1.36 | 270 | 150 | 69 | 376 | 133 | 2.83 |
| Mar. 6......... | A | 265 | 26.5 | 165 | 55 | 527 | 984 | .54 | 325 | 230 | 102 | 435 | 355 | 1.22 |
| Mar. 8......... | C | 265 | 26.5 | 190 | 106 | 448 | 866 | .52 | 275 | 193 | 260 | 366 | 524 | 0.70 |
| Mar. 10......... | D | 265 | 26.5 | 115 | 78 | 626 | 1007 | .57 | 335 | 246 | 100 | 317 | 169 | 1.88 |
| Average... | | ... | .... | 135 | 64 | 478 | 772 | .75 | 301 | 205 | 133 | 374 | 295 | 1.66 |

TABLE 18.—*Effect upon volume of urine and elimination of nitrogen and sodium chloride of solutions of dextrose introduced by rectum. (Values per hour.)*

| Date. | Subject. | Solution injected. | | Preliminary urine (before dextrose given.) | | | | | Experimental urine (before and after dextrose given.) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Volume. | Weight of dextrose. | Length of period. | Volume. | Nitrogen. | NaCl. | Ratio $\frac{N}{NaCl}$ | Length of experimental period. | Portion of period after dextrose injected. | Volume. | Nitrogen. | NaCl. | Ratio $\frac{N}{NaCl}$ |
| | | *c. c.* | *grams.* | *min.* | *c. c.* | *mg.* | *mg.* | | *min.* | *min.* | *c. c.* | *mg.* | *mg.* | |
| 1916 | | | | | | | | | | | | | | |
| May 4 | A | 500 | 30 | 195 | 29 | 462 | 478 | 0.97 | 340 | 245 | 66 | 298 | 123 | 2.42 |
| May 6 | A | [a]500 | 30 | 45 | 69 | 668 | 778 | .86 | 410 | 312 | 116 | 451 | 477 | .95 |
| May 16 | A | [a]500 | 30 | 250 | 45 | 652 | 619 | 1.05 | 290 | 245 | 59 | 499 | 321 | 1.55 |
| 1917 | | | | | | | | | | | | | | |
| Apr. 17 | C | 500 | 30 | { 95 | 27 | 454 | 274 | 1.65 | ... | ... | ... | ... | ... | .... |
| | | | | 215 | 136 | 597 | 474 | 1.26 | 310 | 258 | 38 | 407 | 461 | .88 |
| Apr. 19 | C | 500 | 30 | { 85 | 72 | 570 | 1,084 | .53 | ... | ... | ... | ... | ... | .... |
| | | | | 202 | 156 | 464 | 575 | .81 | 301 | 293 | 67 | 404 | 895 | .45 |
| 1916 | | | | | | | | | | | | | | |
| May 9 | A | 510 | 30 | 170 | 67 | 501 | 643 | .78 | 355 | 254 | 44 | 372 | 215 | 1.73 |
| May 11 | C | 510 | 30 | 460 | 57 | 489 | 942 | .52 | 325 | 218 | 84 | 447 | 471 | .95 |
| May 15 | D | 510 | 30 | 75 | 32 | 314 | 592 | .53 | 340 | 244 | 125 | 470 | 652 | .72 |
| 1917 | | | | | | | | | | | | | | |
| Feb. 22 | A | 520 | 30 | 780 | 23 | 375 | 255 | 1.47 | 600 | 384 | 81 | 390 | 605 | .64 |
| Average | | ... | ... | 266 | 68 | 502 | 595 | .92 | 363 | 273 | 76 | 415 | 469 | 1.14 |

[a] The dextrose was given in a 5 per cent solution of alcohol instead of in the 0.6 per cent solution of sodium chloride used for introducing the dextrose in the other experiments included in this table.

It should be noted that although in two of the experiments the dextrose was injected in a 5 per cent alcohol solution instead of in a 0.6 per cent solution of sodium chloride, the results for all the factors in these two experiments are not significantly different from those in the majority of the other experiments. The sodium-chloride elimination and nitrogen elimination apparently decreased about the same degree in both experiments, as there was no large difference between the ratio of nitrogen to sodium chloride for the preliminary and experimental urines. Following the injection, the volumes of urine were slightly higher in one case than in the preliminary period, and materially higher in the other case, which is somewhat in line with the other experiments. Apparently, in these two experiments, the dextrose was more effective in the regulation of the liquids in the body than was the alcohol.

Two experiments are really too few from which to draw conclusions, but they suggest the importance of carrying out experiments in which alcohol is ingested with a sugar to find whether the effect of alcohol is specifically different when ingested alone from that when it is ingested with sugars.

## Effect on Urine of Rectal Introduction of a Solution of Levulose.

In 10 experiments levulose was given rectally and in a 0.6 per cent solution of sodium chloride. The results are grouped in table 19 according to the amount of levulose given. In the first group of 4 experiments, 25 grams of sugar were given in a volume of 500 c. c., and in the other 6 experiments all but one were made with 50 grams of levulose and volumes of 500 and 1,000 c. c.

With the 25 grams of levulose, the length of the preliminary period averaged 181 minutes and the volume of urine only 49 c. c. per hour, which was rather lower than in most of the preceding groups. The nitrogen output per hour was 455 mg., while that of the sodium chloride was 610 mg. The ratio of nitrogen to sodium chloride was 0.85.

The length of the experimental period was 322 minutes. Of this, 206 minutes were subsequent to the beginning of the rectal injection. The volume of urine was 55 c. c. per hour, only a slight change from that of the preceding period. The nitrogen output per hour averaged 362 mg., a decrease of 93 mg. per hour from the nitrogen found for the preliminary period, while the sodium-chloride excretion averaged 244 mg., or a decrease of 366 mg. per hour from the preliminary value. The ratio between the nitrogen and the sodium chloride was 1.70, indicating that when the values for the preliminary and experimental periods are compared for these two factors it is found that both excretions diminished in the experimental period, but the decrease in the sodium-chloride excretion was greater than the decrease in the nitrogen excretion.

With the group of 6 experiments in which the larger amount of levulose was given, the preliminary period averaged 159 minutes and the volume of urine per hour 70 c. c. The nitrogen per hour was 513 mg., while the sodium chloride reached the very high average value of 1,125 mg. In 3 of the experiments the sodium-chloride elimination was over 1 gram per hour. This large elimination consequently lowered the ratio between nitrogen and sodium chloride to 0.54.

The length of the experimental period was 291 minutes, the part following

TABLE 19.—*Effect upon volume of urine and elimination of nitrogen and sodium chloride of levulose solution introduced by rectum.* (*Values per hour.*)

| Date. | Subject. | Solution injected. | | Preliminary urine (before levulose given). | | | | | Experimental urine (before and after levulose given). | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Volume. | Weight of levulose. | Length of period. | Volume. | Nitrogen. | NaCl. | Ratio $\frac{N}{NaCl}$ | Length of experimental period. | Portion of period after levulose injected. | Volume. | Nitrogen. | NaCl. | Ratio $\frac{N}{NaCl}$ |
| 1916 | | c. c. | grams. | min. | c. c. | mg. | mg. | | min. | min. | c. c. | mg. | mg. | |
| Feb. 1 | C | 500 | 25 | 145 | 26 | 463 | 320 | 1.45 | 325 | 210 | 20 | 404 | 151 | 2.68 |
| Feb. 7 | C | 500 | 25 | 252 | 47 | 502 | 834 | .60 | 318 | 212 | 32 | 375 | 196 | 1.91 |
| Feb. 3 | D | 500 | 25 | 190 | 44 | 439 | 589 | .75 | 305 | 197 | 66 | 370 | 277 | 1.34 |
| Feb. 11 | D | 500 | 25 | 135 | 78 | 417 | 698 | .60 | 340 | 203 | 103 | 300 | 352 | .85 |
| Average | | .... | .... | 181 | 49 | 455 | 610 | .85 | 322 | 206 | 55 | 362 | 244 | 1.70 |
| Feb. 15 | C | 750 | 37.5 | 200 | 118 | 864 | 1,053 | .82 | 285 | 168 | 96 | 429 | 167 | 2.57 |
| Jan. 25 | C | 1,000 | 50 | 225 | 47 | 520 | 721 | .72 | 310 | 207 | 27 | 137 | 202 | .68 |
| Jan. 28 | D | 1,000 | 50 | 145 | 28 | 277 | 502 | .55 | 275 | 139 | 19 | 242 | 265 | .91 |
| Jan. 15 | A | 500 | 50 | 115 | 35 | 297 | 596 | .50 | 280 | 182 | 81 | 381 | 317 | 1.20 |
| Jan. 18 | A | 500 | 50 | 135 | 56 | 397 | 2,467 | .16 | 405 | 275 | 84 | 333 | 403 | .83 |
| Jan. 12 | C | 500 | 50 | 135 | 136 | 721 | 1,408 | .51 | 190 | 89 | 136 | 403 | 483 | .83 |
| Average | | .... | .... | 159 | 70 | 513 | 1,125 | .54 | 291 | 177 | 74 | 321 | 306 | 1.17 |

the levulose injection being 177 minutes; both of these were slightly lower than in most of the preceding groups. The volume of urine per hour averaged 74 c. c. as compared with 70 c. c. in the preliminary period, while the nitrogen excretion per hour was very materially lower—321 mg. as compared with 513 mg. The sodium chloride per hour likewise decreased, with an average of but 306 mg. The ratio of nitrogen to sodium chloride of 1.17 showed no characteristic change.

The findings in the values for the nitrogen elimination after the injection of levulose are of interest because of the materially decreased elimination. They would point to the possibility of levulose acting as a sparer of protein. The indications are, however, that levulose is not actually metabolized immediately when injected by rectum. Consequently, it is a problem as to what the mechanism is by which the rectal injection of levulose can result in a sparing action upon protein metabolism.

*Summary of results on urines of preliminary periods.*—While the preliminary periods in the second group of levulose experiments present an exceptional value for the ratio between nitrogen and sodium chloride, it has been frequently shown in the preceding discussion that the values of one group of preliminary periods were comparable with values in the preceding or following groups. It was not originally intended in collecting these urines in the preliminary periods to secure values for normal urine excretions, but mainly to obtain a basis for estimating the effect of the rectal injection of the different substances upon the volume, nitrogen, and sodium chloride. If, however, the averages of the values in the preliminary periods were markedly different in one group than in another, it would be questionable whether one could compare, for example, the rectal injection of a sodium-chloride solution with the effect of rectal injection of alcohol or sugar solutions. An examination of the several tables shows that there are marked individual variations in any single group by itself. These may be due to inaccuracies on the part of the subjects who reported the times of previous urinations; they may be due to the effect of the preceding diet, which varied in character; or they may be caused by variations in the water balance and equilibrium in the body, which might be variously affected by the rectal injection according to whether the body was in a partially dehydrated condition or supplied with a surplus of water.

The number of experiments in the several groups varied from 4 to 14 and the length of the preliminary periods varied on the average from 135 to 266 minutes. The value of 266 minutes is found in the dextrose series and is high because of the inclusion of the experiment on February 22 in which the length of the preliminary period was 780 minutes. If this figure is excluded, the average for the dextrose experiments is 202 minutes which is close to the general average (193) of the various groups. It will thus be seen that the preliminary urines covered in general a range of time which is fairly comparable from one group to another. The average volume for the 8 groups was 57 c.c. per hour, while the range is from 42 c.c. in the second group of experiments in which 7.5 per cent alcohol was injected to 70 c.c. in the second group with the rectal injection of levulose. The range is not wide considering that the groups varied in the number of experiments and that the experiments in the different groups are not proportionately well divided among the 3 or 4 subjects. The average nitrogen elimination of all the groups is 489

mg. per hour, while the range is from 455 to 531 mg. per hour. The variations from the average are uniform, that is to say, 4 of the group are above the average and 4 are below. The average sodium chloride per hour of all the groups was 706 mg. The range was 574 to 1,125 mg. per hour. The latter value is in the second group of levulose experiments in which the sodium-chloride elimination in the preliminary period is distinctly high in 3 of the 6 experiments.

The ratio of nitrogen to sodium chloride is on the average in the 8 groups 0.84, the range being from 0.54 to 0.99. The lower value is found with the second group of levulose experiments and is due to the very high elimination of sodium chloride in this group. Excluding this value the range is from 0.75 to 0.99, a rather narrow range considering that this is a ratio between two entirely different substances, one of which comes from a material which enters into the metabolism, namely protein, and the other (sodium chloride) has much to do with the equilibrium of fluids. It would seem as though this ratio would be of value in indicating, in any data which are gathered, as to whether there is an abnormal condition of the diet and metabolism with regard to either nitrogen or sodium chloride.

This examination of the preliminary averages and ranges shows that in general these groups are sufficiently similar to be termed comparable and that therefore the data were obtained from urines which were secreted under, on the average, similar conditions. This fact is of importance because significance can then be attached to any material changes which occur in the group figures for the experimental urines as the result of the injection of the various solutions. Changes have more significance when it is recalled that a portion of the experimental period includes urine which was secreted before the injection began.

## Percentile Changes in Urinary Volume, and in Elimination of Nitrogen, and of Sodium Chloride as Affected by Rectal Injection.

In order to bring out more clearly the relative as well as the absolute changes in elimination of sodium chloride and nitrogen, and the changes in volume of urine after rectal injection of various substances, a summary table of the percentile increases or decreases in these quantities has been made. (See table 20.) This records the kind of material injected, the volume of the injection, the weight of the substance in the injection, the number of experiments included in the summary for each substance, the average length of the preliminary period, and finally the average length of the second or experimental period, which included the time after the rectal injection. The percentage of this latter period which was occupied by the time after injection is likewise given.

The last 8 columns of the table record the percentile changes in the elimination for the three quantities—volume, nitrogen, and sodium chloride, and also the percentile changes in the nitrogen to sodium chloride ratio. Under each of these four heads the average change is expressed in two ways: (1) a simple arithmetical average or mean, calculated without regard to sign; and (2) an algebraical average in which the plus and minus signs are taken into consideration in totaling and averaging the individual values. The first indicates the general *amount* of variation, and the second the

TABLE 20.—*Summary table of percentile changes in volume of urine, and elimination of nitrogen and sodium chloride after rectal injection of various substances in solution.*

| Substance in solution. | Volume of solution injected. | Weight of substance. | No. of experiments. | Length of preliminary period. | Length of experimental period. | Proportion of expt. period after injection began. | Percentile changes in elimination for experimental period. | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Volume of urine. | | Nitrogen. | | Sodium chloride. | | Ratio $\frac{N}{NaCl}$ | |
| | | | | | | | Average without regard to sign.[a] | Average with regard to sign.[a] | Average without regard to sign.[a] | Average with regard to sign.[a] | Average without regard to sign.[a] | Average with regard to sign.[a] | Average without regard to sign.[a] | Average with regard to sign.[a] |
| | *c. c.* | *grams.* | | *min.* | *min.* | *p. ct.* | *p. ct.* | *p. ct.* | *p. ct.* | *p. ct.* | *p. ct.* | *p. ct.* | *p. ct.* | *p. ct.* |
| Sodium chloride....... | 220 to 520 | 1.3 to 3.1 | 13 | 239 | 311 | 52 | 70 | + 52 | 25 | + 2 | 62 | —32 | 185 | +171 |
| Alcohol (5 p. ct.)....... | 300 520 | 16.0 26.0 | 14 | 232 | 290 | 65 | 161 | +157 | 17 | — 5 | 65 | —25 | 155 | +135 |
| Alcohol (7.5 p. ct.)..... | 265 500 | 19.9 37.5 | 5 | 179 | 321 | 76 | 193 | +193 | 17 | — 9 | 49 | —49 | 89 | + 89 |
| | 500 | 37.5 | 5 | 160 | 676 | 71 | 47 | + 47 | 25 | —19 | 81 | —81 | 362 | +362 |
| Alcohol (10 p. ct.)..... | 260 to 265 | 26.5 | 4 | 135 | 301 | 68 | 141 | +141 | 26 | —16 | 46 | —46 | 99 | + 99 |
| Dextrose............ | 500 520 | 30.0 | 9 | 266 | 363 | 76 | 109 | + 73 | 25 | —13 | 54 | — 9 | 64 | + 25 |
| Levulose............ | 500 | 25.0 | 4 | 181 | 322 | 64 | 34 | + 7 | 21 | —21 | 58 | —58 | 106 | +106 |
| | 500 to 1,000 | 37.5 to 50.0 | 6 | 159 | 291 | 60 | 46 | + 15 | 38 | —28 | 67 | —67 | 151 | +149 |

[a] The average without regard to sign is simply an expression of the average variation of the results obtained in the experimental period from those of the preliminary period, while the average with regard to sign expresses the directional effect of the solution, that is to say, it shows whether the excretion is diminished or increased in the experimental period as compared with the preliminary period.

general *direction* of the variation. The average without regard to sign is of importance in that it indicates the degree of significance to be attached to the directional effect as shown by the average with regard to sign. That is to say, when the directional effect is accompanied by a considerably larger average without regard to sign, thus showing a large amount of fluctuation in plus and minus values, the average with regard to sign has less significance than would be the case if the two averages were more nearly alike.

From table 20 we find that the number of experiments in the several groups differed somewhat, ranging from 4 to 14 experiments. While the average lengths of the preliminary periods varied from 135 minutes to 266 minutes, their durations are, in general, sufficiently uniform for purposes of comparison. Omitting the 676 minutes of the all-night experiments with 7.5 per cent alcohol solution, we find that the lengths of the experimental periods varied from 290 minutes to 363 minutes. The proportion of the total experimental period which is represented by the period after the injection began ranged on the average from 52 to 76 per cent, which is in general somewhat narrow.

## PERCENTILE CHANGES IN VOLUME OF URINE.

The percentile changes in the volume of urine may first be considered. It must be recognized that, other things being equal, if a quantity of liquid is injected into the body, there will follow, some time or other, the elimination of this quantity of liquid or similar quantities in order to maintain an equilibrium of fluid. The quantity of solution injected in these experiments varied from 220 c. c. to 1,000 c. c. It must also be recalled that in the sodium chloride, dextrose, and levulose experiments, the solution contained the equivalent of 0.6 per cent sodium chloride, while this was absent from the alcohol solution. One would therefore anticipate a difference in the character of the urine eliminated according to whether or not the original solution contained sodium chloride.

In the experiments with a sodium-chloride solution, there was, on the average, a change in volume of ±70 per cent. When the plus and minus signs are taken into consideration in calculating the average, a directional effect of +52 per cent is obtained, i. e., a positive increase in volume. This change is confirmed by the fact that in only 4 of the 13 experiments was there an actual decrease in volume.

The change in the elimination of urine after the injection of 300 to 520 c. c. of a 5 per cent alcohol solution was, on the average, ±161 per cent. This is practically an increase, as, taking into account the small decrease in the experiment with B on October 17, and that with C on November 8, we find the algebraic average to be +157 per cent.

With a 7.5 per cent alcohol solution, all of the experiments in the first group indicated an increase in the volume of urine and thus both the arithmetical and the algebraic averages show a positive change of +193 per cent. The entire group of night experiments in which the 7.5 per cent alcohol solution was given likewise gave increased volumes of urine in the experimental periods, but on a lower level than the shorter experiments, the average increase being but +47 per cent. We may conclude, therefore, that if the urine is measured for a short time after a 7.5 per cent alcohol solution is injected, there is a very marked increase in the volume of urine eliminated, but if the time is extended

somewhat before the urine is finally voided, the increase is not so great. It would thus appear that this effect of the alcohol continues not more than 3 or 4 hours.

With the injection of 265 c. c. of a 10 per cent alcohol solution in 4 experiments, there was an average change of 141 per cent in the volume of urine eliminated. This was a positive increase in volume in all four cases.

When 30 grams of dextrose were injected in 500 to 520 c. c. of a 0.6 per cent solution of sodium chloride, the average change without regard to sign was ±109 per cent. Taking into consideration the plus and minus signs, however, we find that there was an average increase in volume in the experimental period of 73 per cent, that is, there was a greater elimination of urine with a rectal injection of the dextrose solution than there was without it. On the other hand, of the 9 dextrose experiments, there were 3 in which the volume of urine was less than in the preliminary period. Furthermore, in two of the remaining 6 experiments, the dextrose was combined with a 5 per cent alcohol solution; consequently, in these two experiments (with A on May 6 and May 16) the effect of the alcohol upon the volume of urine eliminated shown in the preceding groups of experiments must be taken into consideration. While the algebraic average for the entire group is +73 per cent, rather than ±109 per cent, it would hardly be wise to draw a general conclusion that there was actually an average positive increase in the volume of urine eliminated as a result of the rectal injection of the dextrose solution.

The levulose experiments are averaged in two groups, those with 25 grams of levulose in a 500 c. c. solution and those with 50 grams (including one, also, with 37.5 grams) in a 500 to 1,000 c. c. solution. In the first group, there was a change in volume of ±34 per cent, but when the direction of the change is regarded, it is found that actually there was a change of only +7 per cent in the volume. The individual experiments are equally divided as to the character of the effect; consequently it is doubtful if with this amount of levulose the change in the volume is positive one way or the other, and the direction of the change may depend entirely upon the conditions of the experiment.

With the larger amounts of levulose there was an average change in volume of urine of ±46 per cent or, when the direction of the effect is noted, of +15 per cent. But here again, since in 3 of the experiments a decrease in volume was found, in 2 an increase, with no change in the sixth experiment, it is clear that there was no positive change in one direction or the other during the experimental period.

The general conclusion may be drawn from these findings in respect to changes in volume of urine as a result of rectal injection of various substances that the alcohol solution produced the most positive increase in the volume of urine when it was given by this method. The 0.6 per cent solution of sodium chloride ranks next with a positive change in the majority of instances, and dextrose produced a positive change in many instances. Levulose was, on the whole, neither negative nor positive with respect to change in volume with rectal injection.

It may be concluded, therefore, that alcohol in concentrations varying from 5 to 10 per cent, when injected rectally, acts as a diuretic and increases the volumes of urine eliminated. As alcohol is metabolized, this increase is apparently a specific effect of the alcohol itself and not an accompaniment of

metabolism. Neither is it an increase in volume for the purpose of eliminating foreign substances, such as $\beta$-oxybutyric acid in diabetes.

One would expect that the injection of a 0.6 per cent sodium-chloride solution would not change the volume of urine eliminated, as this would be the introduction into the body of a fluid which was already present in equilibrium with the body-fluids. An increase in the volume of urine eliminated would therefore be an indication that a superfluous amount of liquid had been supplied to the body, and accordingly water had to be eliminated. This subject is of interest in connection with the relieving of thirst by rectal injection, this method or intravenous introduction being usual when fluids can not be introduced by mouth.

As will be seen later, there is an indication that the dextrose introduced rectally is actually metabolized. Consequently, the fluid in the solution need not be retained, for when the dextrose is used, the water in the solution would be more than is needed for maintaining the equilibrium and consequently it would be excreted. The results obtained with dextrose give somewhat unusual significance to the small change in volume of urine which is found when levulose solutions are introduced. In 5 out of 10 of the levulose experiments, the volume excreted after the injection was less than the volume excreted before the injection, showing a retention of fluid when levulose was introduced. Whether this indicates that the liquid was retained because the levulose was not used, or whether such retention is an accompaniment of metabolism—which are as yet but hypotheses—cannot be ascertained from these experiments alone.

Simultaneous determinations of the levulose in the blood, the absorption from the rectum, the volume of urine, and the freezing-point of urine and blood, and also a determination of the respiratory exchange, would be needed in order even to approximate a solution of this problem. It is evident that levulose, when introduced rectally, behaves differently from dextrose so far as the matter of liquid equilibrium in the body is concerned, and one must infer that there is a difference in the character of the metabolism between the two sugars with this method of introduction.

## PERCENTILE CHANGES IN NITROGEN ELIMINATION.

The average changes in the nitrogen elimination with the injection of a sodium-chloride solution is $\pm 25$ per cent, but expressed algebraically it is only $+2$ per cent. Of the 13 experiments, 4 showed an increase of nitrogen with the injection, and the changes are sufficiently large to affect the average for the other 9 experiments in which the nitrogen decreased. Consequently, a rectal injection of sodium chloride has, on the average, no positive effect in increasing or decreasing the nitrogen elimination in these experiments.

When a 5 per cent solution of alcohol was injected, there was an average for 14 experiments of $\pm 17$ per cent in the nitrogen elimination, or $-5$ per cent when the varying signs are taken into consideration. The latter average, though small, really indicates a definite lowering in the nitrogen elimination, inasmuch as but 3 experiments out of the 14 experiments gave an increase in nitrogen elimination.

When a 7.5 per cent solution of alcohol was injected, the average change in nitrogen elimination for the group of shorter experiments was $\pm 17$ per cent, while the average for the group of longer experiments was $\pm 25$ per cent.

Correcting these two averages for the variation in signs, we have −9 per cent for the short experiments and −19 per cent for the night observations. As in the first group there were only two small increases in the individual experiments and in the second group but one small increase, evidently the nitrogen elimination decreased with the injection of a 7.5 per cent solution of alcohol, that is, for a period within 3 to 8 hours after the beginning of the injection.

For 4 experiments in which a 10 per cent alcohol solution was used, with 26.5 grams of alcohol, there was a change of ±26 per cent in the nitrogen elimination. In only one of the 4 experiments was there an increase in the nitrogen output (21 per cent). This group of experiments thus showed an actual decrease of at least 16 per cent in the average amount of nitrogen eliminated within the 3 hours following the injection.

In the 9 experiments with injection of dextrose the average change was ±25 per cent. Correcting for the 2 experiments in which there was an increased elimination gives an average of −13 per cent. The other 7 experiments had a decrease in the nitrogen elimination varying from −9 to −35 per cent, that is, on the whole there was a fall in the nitrogen elimination.

In the first group of experiments with an injection of levulose solution, there was a change of −21 per cent which is representative of the whole group, as in no one of the four experiments was there an increase in the nitrogen elimination in the urine. In the second group of 6 experiments, there was but 1 experiment with an increase in nitrogen elimination (+28 per cent). The general average for the second group was ±38 per cent, with a net change of −28 per cent. This average is larger than that for any of the other groups.

Considering the nitrogen elimination for the whole series of experiments, we find that the injection of the sodium-chloride solution changed it the least, while the use of a 5 per cent alcohol solution produced but little more variation. With the other three groups of alcohol experiments there was a more or less definite decrease in the amount of nitrogen eliminated. With dextrose the average decrease was not so large, but still fairly positive in that there was a lower elimination of nitrogen after the taking of the solution. With the levulose, however, the changes were decisive and probably more marked than with any of the other groups, for there was a definite decrease in the nitrogen elimination in both groups of experiments, with but 1 experiment out of 10 in which there was an increase. With the definite increase in the volume of urine eliminated after the injection of alcohol solutions, one would expect likewise an increased elimination of nitrogen, that is, a washing-out effect. On the contrary, however, there is actually less nitrogen eliminated in the experimental period after rectal injection of alcohol than before, so that the increased volume of urine does not result in an increased nitrogen elimination. The increased volume must, therefore, be due to the specific effect of alcohol upon the water balance itself. It is of interest that the ingestion of a substance like alcohol can actually bring about an increased water elimination without affecting the amount of nitrogen and sodium chloride eliminated. With levulose we have on the other hand a decreased nitrogen elimination without a simultaneous decreased water elimination, and it would seem as though this decrease was actually due to the sparing effect of levulose upon the protein metabolism.

The fact that with levulose the elimination of nitrogen likewise decreased

is rather striking. This decrease cannot be due to a smaller elimination of urine, that is, an actual retention of liquid, as the amount of urine eliminated in the experimental period increased, on the average, over the amount eliminated in the preliminary period (+7 and +15 per cent). It would seem as though the levulose introduced rectally acted as a protective material in the metabolism of protein. In view of the fact that the respiratory exchange of these subjects (see p. 155 ) does not indicate any considerable utilization of levulose in the metabolism, this is rather puzzling. One might conclude that the levulose was deposited as glycogen or was substituted for the carbohydrate already being utilized. However, one would not expect that glycogen deposit or substitution for carbohydrate would result in a decrease in the elimination of nitrogen. At present such decrease can not be explained. Further consideration of the protein-sparing effect of these materials will be given in the final discussion of the results. (See p. 159.)

### PERCENTILE CHANGES IN ELIMINATION OF SODIUM CHLORIDE.

In the experiments in which sodium chloride was injected, its elimination in the experimental period changed on the average ±62 per cent. When corrected for the variation in signs, this average was −32 per cent for the whole group, with but two experiments in which the sodium-chloride elimination actually increased over that in the preliminary period. This occurred in spite of the fact that the sodium chloride injected in the experimental period varied from 1.3 to 3.1 grams, that it was given in an isotonic solution, and that the greater volume of urine might be expected to carry off the surplus sodium chloride. Apparently, however, the salt was retained in the body, or, at least, the effect of the preceding diet was so great upon the elimination of the preliminary period as to cause a much larger output of sodium chloride than during the experimental period, notwithstanding the fact that in the later period sodium chloride was added to the liquids of the body.

When a 5 per cent solution of alcohol was injected in 14 experiments, there was a change in the sodium-chloride excretion of ±65 per cent. When this average is corrected for the increase in 3 experiments, the true average change for the whole group is found to be −25 per cent. Consequently, in this series also there is clearly a reduction in the amount of sodium chloride eliminated. Here, however, we must recall the fact that the solution injected contained no sodium chloride and that the decrease may be a natural one resulting from the diminishing effect of the preceding diet. With a 7.5 per cent alcohol solution there was a consistent lowering in the amount of sodium chloride eliminated in both groups, so a consideration of the direction of the change does not affect the average result. For the first group it was −49 per cent and for the other −81 per cent. These large changes may be due not only to an actual decrease in elimination as a result of a depleted store, but also to an attempt to conserve the sodium chloride present in the body.

With the 10 per cent solution of alcohol a like picture is shown, namely, a consistent decrease in elimination, with an average change of −46 per cent.

With the dextrose usually given in a sodium-chloride solution, there was an average excretion of sodium chloride of ±54 per cent. In 3 of the 9 experiments, the output of sodium chloride increased in the experimental period, so that the average when calculated algebraically was lowered to −9

per cent. It would appear, therefore, that in the majority of cases the elimination of sodium chloride decreased, but this decrease does not seem so definite or regular as with the preceding alcohol groups.

When levulose was given in a sodium-chloride solution, the elimination of sodium chloride averaged −58 per cent in one group and −67 per cent in the other. The picture was entirely consistent throughout each group.

### PERCENTILE CHANGES IN RATIO OF NITROGEN TO SODIUM CHLORIDE.

The nitrogen to sodium-chloride ratio, as explained in the introduction to this section, has probably no profound physiological significance, but is simply a mathematical expression of the change in elimination of nitrogen and sodium chloride in their relationship to one another. Taking the experiments as a whole, we find that the smallest change in this ratio was with dextrose, on the bases of both amount and direction, the actual average with regard to sign being +25 per cent. Interpreting this from the point of view stated above, we may say that with the dextrose solution the rates of change in the eliminations of nitrogen and of sodium chloride were fairly the same. As a matter of fact, in this case the change was slightly greater with the nitrogen elimination, although in the series with the other substances the reverse was true.

The greatest change in the ratio was with 500 c. c. of a 7.5 per cent alcohol solution, the average being +362 per cent, due mathematically to the greater decrease in the elimination of sodium chloride. In considering this ratio it must be remembered that in these experiments the urine after injection was collected subsequent to an all-night period, with an average length of 676 minutes, and that the results were compared with those obtained in a fairly short preliminary period, averaging but 160 minutes.

### SUMMARY OF PERCENTILE CHANGES WITH RECTAL INJECTION.

The most prominent features in the percentile changes of the volume of urine are (1) the decided increase in volume when a solution of alcohol was given alone, which was practically without exception; and (2) the smallest increase in volume when levulose was given in a 0.6 per cent solution of sodium chloride (+7 and +15 per cent). The second statement has the more interest if it be noted that when another carbohydrate was used (dextrose) in a 0.6 per cent solution of sodium chloride, there was an average increase in volume of 79 per cent,[1] whereas when the same solution was given without dextrose, the volume increased on the average 52 per cent. When levulose was added to the sodium-chloride solution, therefore, the change in volume was least, whereas when another carbohydrate (dextrose) was combined with the sodium chloride, the volume of urine did not decrease, but, if anything, it was increased.

With the nitrogen elimination the two striking points are the very small average increase when a sodium-chloride solution was given alone and a uniformly average decrease in the nitrogen elimination with the other groups of experiments, particularly when levulose was given in a sodium-chloride solution. The changes with dextrose and with alcohol solutions were in the same direction as those for levulose, but were not so large.

[1]In calculating the percentage for this comparison, the two experiments in which an alcohol solution was used (May 6 and 16) were omitted.

In the elimination of sodium chloride there was a very small percentile change when dextrose was given in a 0.6 per cent solution of sodium-chloride and a much greater decrease with levulose in the same medium. In other words, the general picture indicates that the transport and metabolism of dextrose were specifically different from those of levulose as regards the equilibrium of sodium chloride and the volume of liquid in the body. One might possibly anticipate here an hypothesis which will be discussed later, namely, that a dextrose solution, when injected rectally, is actually utilized and burned, while a levulose solution is stored in the tissues and is not metabolized in the same way as when it is introduced by mouth. (See p.187.)

The alcohol solution brought about an actual increase in the elimination of urine, but not a corresponding change in the sodium chloride in the body. This is contrary to what one would expect, for, since alcohol has a diuretic effect, it would be supposed that this salt would be washed out with the water. Apparently, however, the effect of alcohol is to deprive the tissues of water and to cause its elimination without removing other constituents at the same time. Theoretically, this would mean an actual increase in the concentration of sodium chloride in the system. It is evident from the experimental results reported here that the problem of the effect of the rectal injection of various substances needs considerable further study in regard to the volume and composition of the urine and equilibrium of salts and liquids in the body. It is conceivable that the rectal introduction of liquids containing electrolytes and metabolites may present an entirely different set of conditions for adjustment in the matter of equilibrium in the body liquids from those with the same liquids introduced by mouth. It has been found, for example, that the introduction of sodium bicarbonate rectally produces a greater change in the hydrogen-ion concentration than the same material introduced intravenously.[1] An investigation of this character suggests the opportunity for considerable work upon the difference in both equilibrium and metabolism with the two methods.

## RESPIRATORY EXCHANGE WITH RECTAL INJECTION.

One of the main purposes of this whole investigation was to determine whether or not alcohol is actually utilized when introduced rectally. To this end it was necessary to find whether the character and the amount of the metabolism were affected by such injection.

The respiratory quotient is usually considered an index of the character of the material utilized in the body, for it is ordinarily the resultant of the katabolism of protein, fat, and carbohydrate. The general range of the quotient is from 0.71 for fat to 1.00 for carbohydrate. With a post-absorptive subject, the quotient commonly varies between 0.75 and 0.90. The respiratory quotient of ethyl alcohol is 0.667, so that when a considerable amount of alcohol is utilized in the metabolism, theoretically it tends to lower the quotient, regardless of whether it replaces but one substance or a combination of substances. Replacement of fat by alcohol lowers the quotient least, while the replacement of carbohydrate by alcohol lowers it most. Accordingly, whatever the change may be that takes place, the ultimate effect of the util-

[1] Milroy: Journ. Physiol., 1917, 51, p. 281.

ization of alcohol in the metabolism must theoretically be a lowering of the respiratory quotient.

When various foodstuffs are ingested by mouth, there is nearly always an increase in the total metabolism which varies with the kind and amount of food taken. It is therefore conceivable that alcohol when metabolized will tend to raise the metabolism. A rise or a lowering of the metabolism is usually accompanied by a similar change in the pulse-rate.

The problem in these studies, therefore, was to determine, by measurement of the respiratory exchange, whether, after the rectal injection of alcohol, the respiratory quotient indicated that alcohol had been utilized and whether the metabolism had been stimulated, also to note whether any changes in the metabolism were accompanied by changes in pulse-rate.

Sugars are substances which cause a rise in the respiratory quotient when they are taken by mouth. Levulose and sucrose are most effective in this respect, while the change after dextrose depends upon the previous storage of carbohydrates in the body. This research with rectal injection was therefore extended to include studies with levulose and dextrose to find if their rectal injection produced changes in the respiratory quotient of like character and magnitude to those obtained when these two substances are taken by mouth.

Little or nothing is known concerning the effect upon the respiratory exchange of this method of introduction of liquids into the body, i. e., by rectum. Since it was necessary to distinguish between the influence of the method, if any, and the effect of the substance injected, studies were made in which different volumes of a weak solution of sodium chloride (0.6 per cent) were injected rectally. These experiments served a double purpose in that they also acted as a control upon the trend of the respiratory exchange during the period of the day in which most of the alcohol and sugar experiments were made.

The general plan of the studies of respiratory exchange and the methods employed have already been outlined. (See p. 24.) The four medical students used as subjects, A, B, C, and D, have likewise been described. (See table 1, p. 22.) Subject B was employed only in the experiments with sodium chloride and with the 5 per cent alcohol solution. The two series with this subject were unsatisfactory as a whole, because of the variability of the subject's temperament, and also because of the brevity of the experiments. The results of these observations with B have therefore been omitted from the discussion of the respiratory exchange, although his data have been included in the absorption and urine studies.

As a rule, the subjects came to the Laboratory late in the afternoon, either without food since breakfast or, in the later experiments, with but a light lunch at midday. After the preliminary flushing of the rectum and the lower intestine, the minor recording appliances were adjusted and the subject placed himself in position for the respiration experiment. For the most part the gasometer method of measurement was used (see p. 24), the breathing appliance being either a mouthpiece or a mask. The former appliance was employed only in the earlier experiments. A few observations were made with the clinical chamber apparatus, and, for comparison, experiments were also carried out in which the substance under investigation was given orally.

Observations of the respiratory exchange and pulse-rate were usually made previous to the injection to provide basis for comparison, as well as during and following the giving of the solution. Occasionally the preliminary periods were omitted in order that the study might be continued for a greater length of time after the injection without fatiguing the subject.

In presenting the results, the general details as to volume of solution, duration of injection, and periods before and after the beginning of the injection are given in tables for the individual series. The experimental data appear in the form of curves indicating for each experiment the general course of the respiratory quotient, the oxygen consumption per minute, and the pulse-rate per minute. These charts show the level of the three factors in the different periods of the experiments before and after the beginning of the rectal injection.

When the mask was used it was possible to make continuous observations, this being clearly shown by the unbroken curves. The interruptions in these curves which occasionally occur are usually due to a temporary discontinuance of the observations for urination, and infrequently to slight adjustments of some of the appliances. Whenever the sleep recorder was used, the tracing is usually reproduced in the figure for assistance in interpreting the various changes in the three factors. The variation in the amount of sleep of the subjects was a disturbing feature of these studies and frequently obscured the true effect of the injection.

The number of periods[1] before injection recorded in the tables includes all those in which measurements were made. In several of the charts, however, only those periods in the half hours immediately preceding the beginning of the injection are plotted. In some cases, the subject was not allowed the customary half hour of rest before the initial measurement, but the experiment was begun as soon as the man lay down. The metabolism of the subject was not therefore at a standard level, and there was usually an immediate sharp decline in the oxygen absorption and pulse-rate in the first portion of the experiment, due to the cessation of the previous muscular activity.

The volume of the solution measured out from the general source of supply for injection was generally about 20 c. c. more than the volume actually injected, this 20 c. c. representing the liquid usually remaining in the catheter and connections at the conclusion of the injection. The total volumes measured are given in the tables as the amount injected, but correction is made for the residue when calculating the amount absorbed.

In discussing the results, the experiments with the sodium-chloride solution are first considered, those with the alcohol solutions in the various concentrations are next presented, and finally those with the two sugars, dextrose and levulose.

[1] The word "period" is used to designate the smallest division of time for which results were obtained. An "experiment" consists of one or more "periods" following one another at short intervals, as in the experiments with the mouthpiece, or succeeding one another without interval, as in the experiments with the mask.

## RESPIRATORY EXCHANGE WITH RECTAL INJECTION OF A SOLUTION OF SODIUM CHLORIDE.

The solution used in the sodium-chloride experiments was the same as that employed as a carrier for the sugars, i. e., a 0.6 per cent concentration of sodium chloride in water. Such a solution is a common medium for the rectal introduction of various substances. A large amount of the material was made up at the beginning of the observations and stored, this being drawn upon as needed for the individual experiments. Both the gasometer method and the clinical respiration chamber were used in studying the effect of rectal injection of a sodium-chloride solution.

### Sodium-Chloride Experiments with Gasometer Method.

In the gasometer series there were 14 experiments (excluding those with subject B), of which 8 were with subject A, 5 with subject C, and 1 with subject D. The general data for these experiments are presented in table 21, and the results of the observations are given graphically in figures 5 to 18.

Table 21.—*Statistics of respiratory exchange observations before and after the injection by rectum of a 0.6 per cent solution of sodium chloride.*

| Subject. | Date. | Amount injected. | Duration of injection. | Periods before injection. | | Periods after injection. | |
|---|---|---|---|---|---|---|---|
| | | | | Number. | Time covered. | Number. | Time covered. |
| | 1915 | *c. c.* | *min.* | | *h. min.* | | *h. min.* |
| A | Oct. 1[a] | 100 | .. | 3 | 0 45 | 12 | 2 32 |
| | | 200 | .. | 9 | 2 29 | 6 | 0 58 |
| | Oct. 15[a] | 300 | 8 | 4 | 0 45 | 11 | 3 8 |
| | Oct. 19[a] | 325 | 8 | 4 | 0 53 | 13 | 2 49 |
| | Nov. 4[a] | 420 | .. | 4 | 1 17 | 11 | 2 38 |
| | Dec. 8[b] | 520 | 23 | 6 | 1 00 | 24 | 3 30 |
| | Dec. 20[b] | 500 | 12 | 11 | 2 8 | 15 | 2 9 |
| | 1916 | | | | | | |
| | Mar. 14[b] | 260 | 17 | 8 | 1 20 | 16 | 2 40 |
| | Mar. 20[b] | 260 | 28 | 10 | 1 48 | 10 | 1 42 |
| | 1915 | | | | | | |
| C | Oct. 16[a] | 320 | 2 | 5 | 1 6 | 6 | 1 21 |
| | Oct. 21[a] | 320 | 4 | 5 | 1 15 | 8 | 2 4 |
| | Nov. 2[a] | 420 | 5 | 5 | 1 8 | 11 | 2 45 |
| | 1916 | | | | | | |
| | Feb. 21[b] | 520 | 30 | 9 | 1 29 | 11 | 1 51 |
| | Mar. 16[b] | 260 | 25 | 7 | 1 10 | 11 | 1 50 |
| D | Apr. 14[b] | 500 | 27 | 8 | 1 17 | 13 | 2 13 |

[a] The mouthpiece and gasometer combination was used, with the subject sitting.
The mask and gasometer combination was used, with the subject lying on a couch.

In the experiment with A on October 1, two injections were given on the same evening, but these were separated by a considerable interval of time (1 hour 45 minutes). The period of flow, which represents the time from the beginning of the injection until its conclusion, varied from 2 to 30 minutes. In a number of the first experiments, the actual time of flow was not recorded,

but as the period of introduction was short in these earlier observations, it is probable that the injection was completed in 5 minutes or less. With alcohol and the sugars, slower rates of rectal alimentation were adopted in the later observations; consequently, the same procedure was followed in the later experiments with the solution of sodium chloride. The measurements of the respiratory exchange were not made continuously until the experiment with A on December 8, which was the first experiment in the sodium-chloride series in which the mask was used as a breathing appliance. Accordingly, in the earlier experiments the average length of the period may not be found by dividing the length of time by the number of periods. The average number of periods before injection in the sodium-chloride series was 6 and the average time covered was 1 hour and 20 minutes. The average number of periods after the beginning of the injection was 12 and the average length of time covered was 2 hours and 17 minutes. The sleep-recording apparatus was used in the experiment with C on February 21, 1916, and in the subsequent experiments with all of the subjects in March and April 1916.

The sodium-chloride experiments were conducted primarily as controls to give results which should serve as a basis of comparison for the results of observations in which alcohol, dextrose, and levulose were injected into the rectum. The three factors particularly observed were (1) the oxygen consumption as a measure of the total metabolism; (2) the pulse-rate for its significance in relation to changes in the total metabolism, as well as the effect upon it of the solution; and (3) the respiratory quotient as an indicator of the utilization of the material injected. Since theoretically the sodium-chloride solution should produce no change that would not take place if no injection were made, any changes which might occur in these three factors after the introduction of the solution should be taken into consideration in interpreting results obtained after the introduction of the other materials employed in this research, and especially those in which a sodium-chloride solution was used as a carrier.

Most of the difficulties encountered in securing comparable results in this series were due, first, to the use of short periods which were not continuous, and second, to the varying conditions as to sleep. The latter had an effect upon the metabolism, particularly in relation to the respiratory quotient, but unfortunately the apparatus for detecting sleep was not applied until the research was more than half completed. Accordingly, as most of the experiments with the solution of sodium chloride were made before this apparatus was introduced, but little data could be had in this series as to the amount of sleep and its effect upon the metabolism. Subject A, particularly, became drowsy even in the early experiments, when he was in the sitting position, and it was repeatedly necessary to urge him to keep awake. In spite of this he frequently fell asleep or was very drowsy, so that the ventilation data were in many cases extremely low. Undoubtedly, also, the change from being awake at the beginning of the observations to sleep near the end affected the respiratory quotient.

The results obtained may be considered first from the standpoint of general level of metabolism as compared with the basal metabolism of the individual. (See table 1, p. 22.) This concerns the values obtained before rectal injection began. Second, the results may be considered from the standpoint of the change in the metabolism which took place after rectal injection began, and

this may be compared to the metabolism in the periods preceding injection. The succeeding portions of time after injection may also be compared with one another. This latter method is necessary in some of the experiments, because there were no periods before rectal injection took place.

The conditions under which these experiments were made differ in several ways from the usual measurements of the "basal" metabolism. In the first place, the subject was not in a strictly post-absorptive condition, because the first observations were begun earlier than 12 hours after the last food. As previously pointed out (see p. 81), at the beginning of the series the subjects had their last meal in the morning, i. e., breakfast. In some cases, however, they departed from this requirement and took food later than the usual breakfast time, e. g., October 15, $10^h\ 00^m$ a. m.; October 19, $10^h\ 30^m$ a. m.; December 20, $9^h\ 30^m$ a. m. Later in the research they were allowed to have food (a lunch) at noon, as it was believed that a light lunch at that time would not have an effect upon the metabolism at $5^h\ 30^m$ p. m., about which time the first measurements began. In general, the latest time that food was taken was at $1^h\ 30^m$ p. m. Subject C on March 16 had a small portion of apple at $2^h\ 20^m$ p. m.

The second unusual condition was the time of beginning the preliminary or base-line measurements, this being in the latter part of the afternoon instead of in the morning, as is the usual procedure. During the day the subjects were occupied in their usual attendance at clinics and lectures and in similar activities incidental to the regular routine of a medical student. When they came to the Laboratory they were, as a rule, more or less fatigued and quite ready for a rest. Their mental condition also varied according to whether the day's work had been one of unusual interest, dry routine, or diversified in character. In the observations reported by Benedict [1] on a fasting man, the values for the oxygen consumption between $7^h\ 00^m$ and $7^h\ 45^m$ p. m. on the twelfth to the thirtieth days of the fast were all higher than those obtained in the morning between $8^h\ 30^m$ and $9^h\ 30^m$ a. m., the increase varying from 1.5 per cent to 10 per cent, the usual increase being about 6 per cent. The course of the metabolism between $5^h\ 30^m$ and $10^h\ 30^m$ p. m. with the subjects of the rectal study could not be predicted.

Another condition which differed from those of most previous work in the measurement of respiratory exchange was that instead of making single isolated periods of measurement, it was almost invariably the case that two and often more periods of 5 to 10 minutes' duration were carried out immediately following one another without an interval between periods.[2] This was the usual procedure in those experiments in which the mouthpiece was used. After 3 to 5 periods of measurement there was an interval which varied in length, but was usually about 30 minutes, and then 3 more measurements were made in the same way. When the mask was used, the periods succeeded one another without interruption from the beginning to the end of the experiment. The individual periods varied from 4 to 15 minutes in duration.

In metabolism measurements as usually made there is a single period of observation varying in length between 5 and 15 minutes, and then an interval

[1] Benedict: Carnegie Inst. Wash. Pub. No. 203, 1915, p. 334.

[2] Higgins (Am. Journ. Physiol., 1916, 41, p. 258), in this Laboratory, carried out a number of experiments with alcohol and sugars in which four successive periods in 15 minutes were made without interruption.

of rest before the next period. With such a routine there is no means of knowing whether in the rest interval the metabolism is the same, either in character or in amount, as in the observation itself. It is barely possible that the subject may rouse himself to the same degree or maintain the same degree of relaxation in each of the observation periods, but during the intervals his condition of tenseness or relaxation, wakefulness, and attention may be quite different from that in the periods themselves. Johansson [1] recognized that it is not feasible for a subject to maintain a uniform condition of complete muscular rest for any great length of time. His usual routine was to have a half hour or an hour of complete muscular rest during which the metabolism measurements were made, followed by a half hour or an hour in which the subject was permitted to move about to some extent; then another experimental period was carried out.

Even with the best conditions of experimental technique, there may be considerable variation from period to period when the experiments consist of isolated periods. This was evident in a study of the respiratory exchange of 17 untrained medical students.[2] Twelve measurements of 10 to 15 minutes' duration followed each other in the morning, with the subject in the post-absorptive condition and with intervals of at least 5 minutes between the periods. The purpose of the study was to compare the respiratory exchange obtained with the Benedict portable apparatus [3] with that obtained from the collection of the expired air in a gasometer [4] and its analysis. Three different breathing appliances (mouthpiece, nosepieces, and mask) were used. The main variation was, therefore, in the techniques used in the different periods. With an average oxygen consumption of 236 c. c., the differences between the maximum and minimum oxygen consumption for the 12 periods varied with the 17 subjects from 12 to 78 c. c. per minute, with an average difference of 33 c. c. per minute.[5] The variations were not always due to differences in technique, as frequently wide differences in oxygen consumption were found with the same apparatus and breathing appliance. Also, they were not due to the varying amount of sleep or drowsiness, as the signal-magnet stimulus was used in every period, to which they responded regularly.

If there are such variations from period to period when the measurements are isolated, it is all the more likely that there will be variations of the same or greater magnitude when they are made continuously over short intervals of time without lapses. The shorter the unit of time and the longer the series, the less likelihood there is of absolute constancy in a physiological process set about with so many variables as may exist in higher biological organisms, such as humans. This is axiomatic. The important point in regard to the experiments here is that with the mouthpiece there was usually a series of three or more periods in succession, and that with the mask the entire experiment of several hours' duration was generally an uninterrupted series of periods varying in length from 5 to 15 minutes. With the latter appliance the metabolism of the subject was therefore being measured in

[1] Johansson: Skand. Arch. f. Physiol., 1908, 21, p. 1.
[2] Hendry, Carpenter, and Emmes: Boston Med. and Surg. Journ., 1919, 181, pp. 285, 334, and 368.
[3] Benedict: Boston Med. and Surg. Journ., 1918, 178, p. 667.
[4] Tissot: Journ. de physiol. et de pathol. gén., 1904, 6, p. 688; Carpenter, Carnegie Inst. Wash. Pub. No. 216, 1915, p. 63.
[5] Hendry, Carpenter, and Emmes: loc. cit., p. 342, table VII.

such a manner as to show all the variations that may occur over a fairly long period of time.

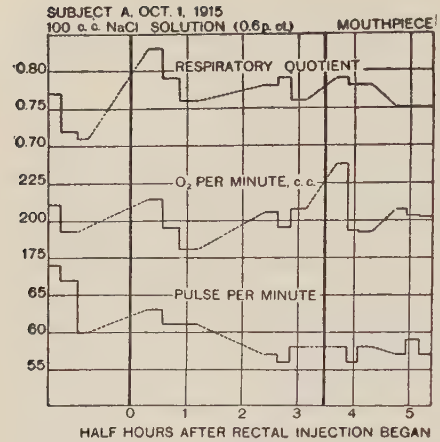
### RESULTS OF MEASUREMENTS BEFORE RECTAL INJECTION.

#### Pulse-Rate.

*Subject A*.—The results of the observations on the pulse-rate in the mouthpiece experiments with subject A are shown in figures 5 to 8. On all of these days there was a preliminary rest period of at least a half hour in which no observations were made of the metabolism. During this period the pulse-rate was recorded, but these values are not plotted on the charts. During the last 15 to 25 minutes of this preliminary rest period there was little or no change in pulse-rate. In two of the experiments, October 1 and November 4, there was a noticeable fall in rate in the first three experimental periods preceding the injection, and in all of the experiments the pulse-rate in the period at or immediately preceding the rectal injection was materially lower than that during the initial periods of the experiments. It is therefore evident that a half-hour preliminary rest was not sufficient for the pulse-rate to reach a basal level at this period of the day, or that there was a factor in the experiments which tended to lower the heart-rate. This factor was probably either drowsiness or the quieting effect of the relaxed condition during the experimental periods. The pulse-rate just before the injection varied from 49 beats on November 4 to 70 beats on October 19. None of these experiments were in the morning and the subject was not in a strictly post-absorptive condition.

The routine in the experiments with the mask in December 1915 and March 1916 (see figs. 9 to 12) differed from those with the mouthpiece in that there was practically no preliminary rest, and the measurements commenced as soon as the subject lay down. As shown in table 21, the preliminary portion (before injection) was over an hour in length. In the figures only the 40 minutes (4 periods) preceding the rectal injection are plotted, so that the average value indicated for the first period in the figures is at least one-half hour after the subject lay down. On March 14 and 20 (see figs. 11 and 12) it is evident from the sleep record that the man was asleep practically the entire experiment. On December 20 the protocols show that he was alternately asleep and awake during the preliminary observations. The pulse-rates varied between 58 and 66 beats in the periods immediately preceding the rectal injection and, in general, the preliminary curves are less variable than those in the experiments with the mouthpiece. The basal pulse-rate (see table 1, p. 22) for this man was 64 beats per minute, so that the rates obtained in this series are close to this value.

*Subject C*.—The pulse-rates for the mouthpiece experiments with subject C are shown in figures 13 to 15. The rates at or immediately preceding the rectal injection vary between 64 and 80 beats. The experiment on October 16 was in the early afternoon. The other two were in the early evening. In all three experiments a half-hour rest period preceded the metabolism observations. The pulse-rates with this subject were more nearly uniform than those of subject A. In the two 1916 experiments with the mask (see figs. 16 and 17) the preliminary periods continued for more than an hour, and the original protocols show that in each experiment there was some sleep. In the period immediately preceding the rectal injection, the values

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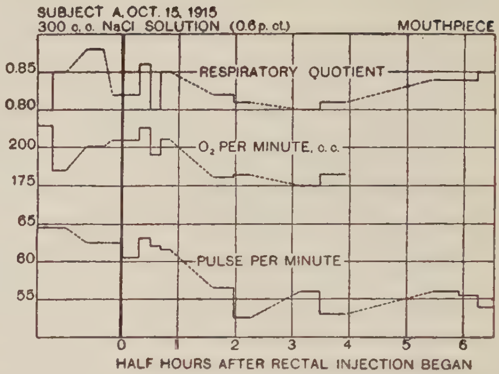


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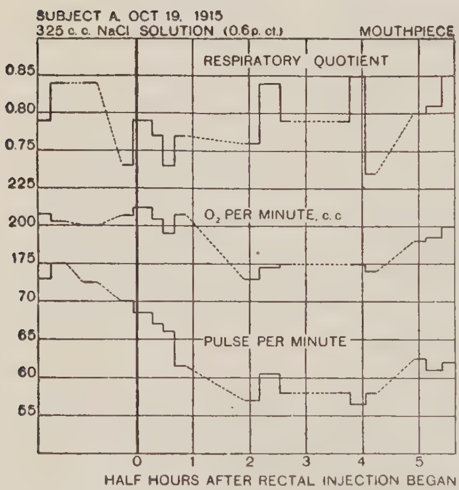
FIG. 5.—Respiratory quotient, oxygen absorption, and pulse-rate of subject A, October 1, 1915, before and after rectal injection of 100 c. c. of a 0.6 per cent solution of sodium chloride, followed by a second injection of 200 c. c. (Mouthpiece, with intermittent observation.)

The solid portions of the three curves represent the averages for the periods and the broken portions the intervals between observations. This applies to all subsequent experiments with the mouthpiece. The two heavy vertical lines indicate the beginning of the first and second rectal injections.

FIG. 6.—Respiratory quotient, oxygen absorption, and pulse-rate of subject A, October 15, 1915, before and after rectal injection of 300 c.c. of a 0.6 per cent solution of sodium chloride. (Mouthpiece, with intermittent observation.)

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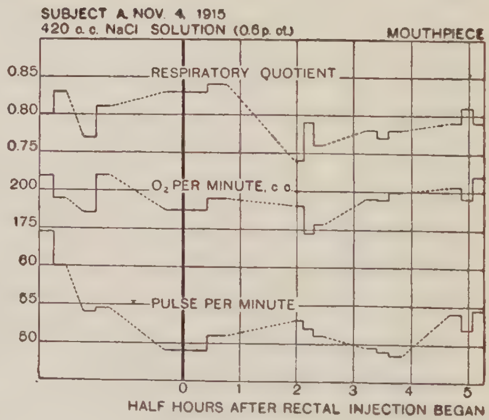


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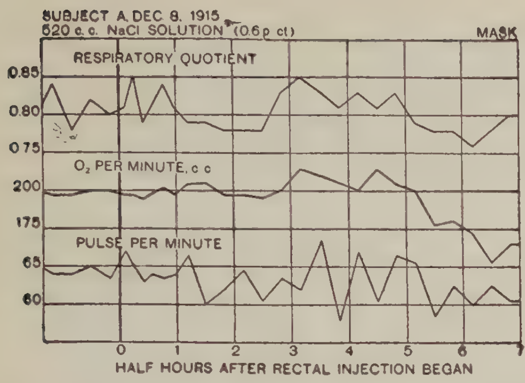
FIG. 7.—Respiratory quotient, oxygen absorption, and pulse-rate of subject A, October 19, 1915, before and after rectal injection of 325 c. c. of a 0.6 per cent solution of sodium chloride. (Mouthpiece, with intermittent observation.)

FIG. 8.—Respiratory quotient, oxygen absorption, and pulse-rate of subject A, November 4, 1915, before and after rectal injection of 420 c. c. of a 0.6 per cent solution of sodium chloride. (Mouthpiece, with intermittent observation.)

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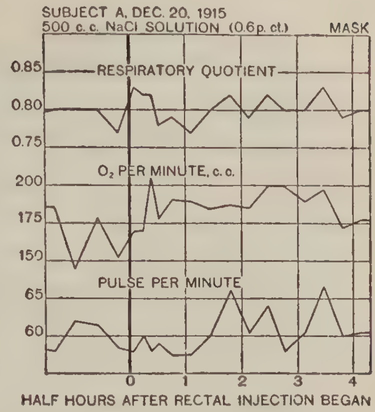


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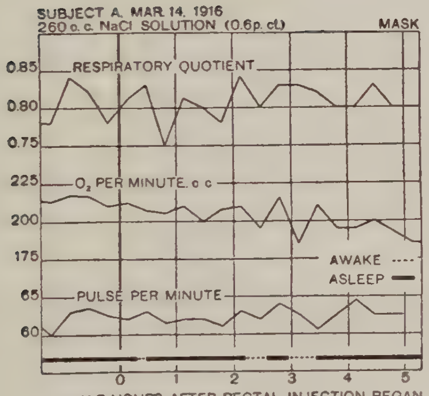
FIG. 9.—Respiratory quotient, oxygen absorption, and pulse-rate of subject A, December 8, 1915, before and after rectal injection of 520 c. c. of a 0.6 per cent solution of sodium chloride. (Mask, with continuous observation.)

FIG. 10.—Respiratory quotient, oxygen absorption, and pulse-rate of subject A, December 20, 1915, before and after rectal injection of 500 c. c. of a 0.6 per cent solution of sodium chloride. (Mask, with continuous observation.)

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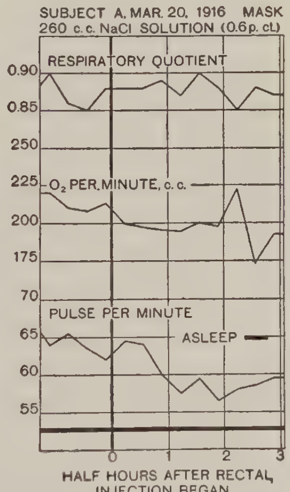


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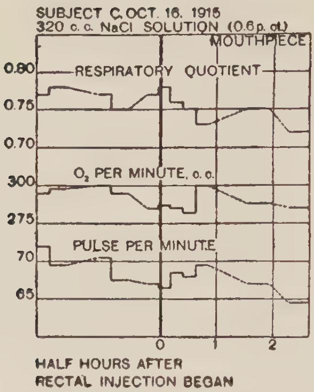
FIG. 11.—Respiratory quotient, oxygen absorption, and pulse-rate of subject A, March 14, 1916, before and after rectal injection of 260 c. c. of a 0.6 per cent solution of sodium chloride. (Mask, with continuous observation.)

The horizontal line at the bottom of this and subsequent charts gives a record of sleep, the solid portions indicating when the subject was asleep, and the broken portions when he was awake.

FIG. 12.—Respiratory quotient, oxygen absorption, and pulse-rate of subject A, March 20, 1916, before and after rectal injection of 260 c. c. of a 0.6 per cent solution of sodium chloride. (Mask, with continuous observation.)

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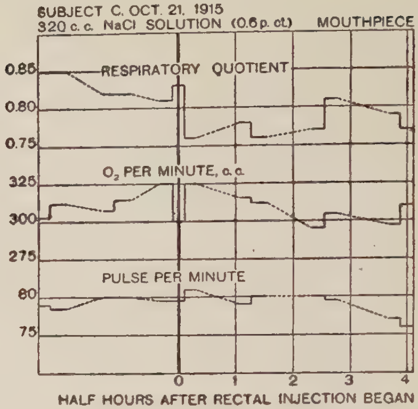


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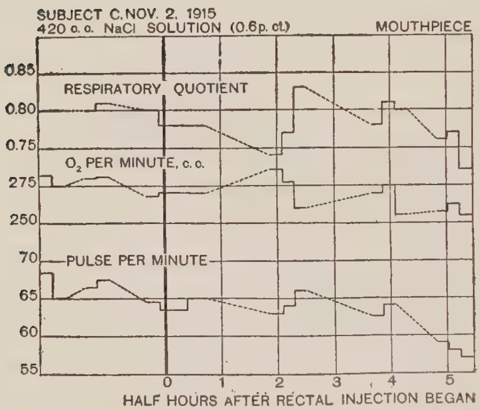
FIG. 13.—Respiratory quotient, oxygen absorption, and pulse-rate of subject C, October 16, 1915, before and after rectal injection of 320 c. c. of a 0.6 per cent solution of sodium chloride. (Mouthpiece, with intermittent observation.)

FIG. 14.—Respiratory quotient, oxygen absorption, and pulse-rate of subject C, October 21, 1915, before and after rectal injection of 320 c. c. of a 0.6 per cent solution of sodium chloride. (Mouthpiece, with intermittent observation.)

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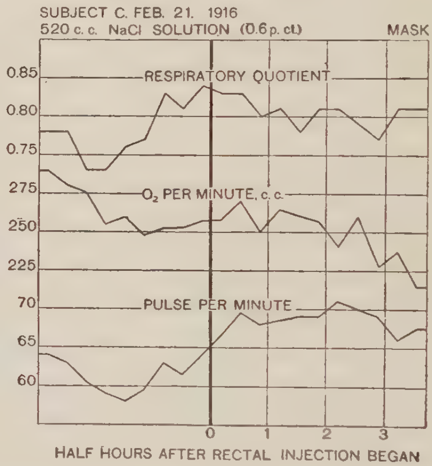


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FIG. 15.—Respiratory quotient, oxygen absorption, and pulse-rate of subject C, November 2, 1915, before and after rectal injection of 420 c. c. of a 0.6 per cent solution of sodium chloride. (Mouthpiece, with intermittent observation.)

FIG. 16.—Respiratory quotient, oxygen absorption, and pulse-rate of subject C, February 21, 1916, before and after rectal injection of 520 c. c. of a 0.6 per cent solution of sodium chloride. (Mask, with continuous observation.)

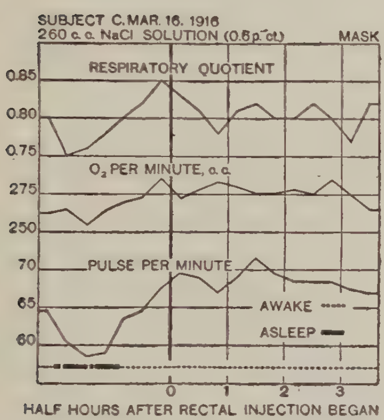
were 64 and 68 beats. The basal pulse-rate (see table 1, p. 22) for this subject was 65 beats per minute.

*Subject D.*—There was only one control experiment with subject D. The observations began about 15 minutes after the subject lay down and are plotted in full in the curve. (See fig. 18.) There was a period of sleep of approximately 30 minutes which produced a marked depression in the pulse-rate, making it difficult to compare the values obtained before and after

rectal injection. At the time rectal injection began, the pulse-rate was 79 beats per minute.

OXYGEN ABSORPTION.

*Subject A*.—In the mouthpiece experiments with subject A (figs. 5 to 8), the greatest range in the oxygen absorption (29 c. c.) was on October 15. The averages for the four experiments are chronologically 202, 201, 205, and 197 c. c. The basal oxygen absorption for this subject was 206 c. c. per minute. (See table 1, p. 22.) In the four experiments with the mask (figs. 9 to 12) there were large fluctuations in the oxygen absorption. The values on December 20 (fig. 10) appear unreasonable because they are so low, even on the average (166 c. c.), and the pre-injection value of 186 c. c. near the beginning of the experiment was probably nearer the truth. The pre-injection

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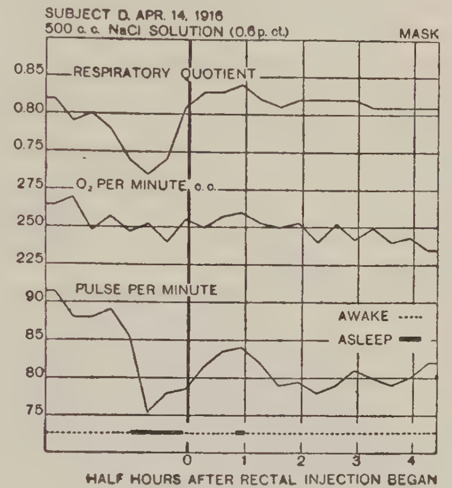


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FIG. 17.—Respiratory quotient, oxygen absorption, and pulse-rate of subject C, March 16, 1916, before and after rectal injection of 260 c. c. of a 0.6 per cent solution of sodium chloride. (Mask, with continuous observation.)

FIG. 18.—Respiratory quotient, oxygen absorption, and pulse-rate of subject D, April 14, 1916, before and after rectal injection of 500 c. c. of a 0.6 per cent solution of sodium chloride. (Mask, with continuous observation.)

averages for the plotted periods in the other mask experiments are 199, 214, and 215 c. c. As will be brought out more fully in the discussion of the respiratory quotient, the picture on March 20 corresponds to that after a carbohydrate meal.

*Subject C*.—Subject C did not vary so widely in his oxygen absorption from period to period as did A, although the values were by no means uniform. The averages for the periods previous to injection in the mouthpiece experiments (figs. 13 to 15) were 296, 312, and 277 c. c. per minute, a rather wide range. On October 21 the oxygen absorption was high and accompanied by a high pulse-rate—79 beats. The basal oxygen value for this subject was 285 c. c. per minute. (See table 1, p. 22.) The variations in the preliminary oxygen values in the two experiments with the mask (figs. 16 and 17) were 41 c. c. and 23 c. c., and the averages for the four periods immediately

preceding the injection were 253 and 273 c. c. per minute. In both experiments there was a short interval of sleep which tended to depress the values slightly.

*Subject D.*—In the one experiment with subject D (fig. 18), there was some fluctuation in the first three periods which were followed by five periods in succession with a narrow range of but 17 c. c. The average oxygen absorption for these five periods was 250 c. c. per minute. No basal values are available for this subject.

### Respiratory Quotient.

*Subject A.*—The respiratory quotients in the four mouthpiece experiments with subject A were extremely variable from period to period before rectal injection began, the greatest range being 0.11 on October 19. Excluding the experiment of October 1, the average values for the periods before injection were normal, being 0.84, 0.80, and 0.81. The respiratory quotients in the four experiments with the mask show a marked degree of variability, although not so great as with the mouthpiece. The average values for the four periods before injection were 0.81, 0.79, 0.81, and 0.87, the latter occurring on March 20. The whole picture of the last experiment (fig. 12) indicates the ingestion of a heavy carbohydrate meal before the experiment began, although the subject reported that the last food taken was 4 hours before he came to the Laboratory. This consisted of broth, mashed potatoes, fish, graham bread, and coffee.

*Subject C.*—In the three experiments with the mouthpiece, the range of quotients was much narrower than with subject A. The average values for the preliminary observations were 0.77, 0.83, and 0.80. In the two experiments with the mask, the figures before rectal injection were markedly influenced by the period of sleep which occurred. This caused a wide range, viz, approximately 0.10 in both experiments. The average of the two periods just before injection began is 0.83 for both days.

*Subject D.*—The range of values before injection took place in the single control experiment with subject D was rather wide, viz, 0.10, this being due to sleep. The value nearest to the time injection took place was 0.81.

### General Conclusions.

To sum up, the measurements of the pulse-rate, oxygen consumption, and respiratory quotient of the three subjects A, C, and D before rectal injection took place show first that one of the subjects, A, gave extremely variable results from period to period in the same experiments, but the average of all the periods in any single experiment is not far from those of the other experiments and reasonably close to the basal value for this subject. Subject C gave less variable results in the individual experiments, but widely varying results among the different experiments. There was only one experiment with D. The causes for these variations are considered to be: (1) inconstancy of subject A; and (2) the conditions under which these experiments were carried out, viz, (*a*) in the evening, (*b*) with varying conditions as to the subject himself, and (*c*) the use of consecutive measurements in groups of periods rather than measurements in single isolated periods. The effect of the rectal injection of sodium-chloride solution therefore has to be considered with respect to the course of the individual experiments and not with respect to the average of all the experiments.

## RESULTS OF MEASUREMENTS AFTER RECTAL INJECTION OF SODIUM CHLORIDE.

### Pulse-Rate.

In all of the four mouthpiece experiments with subject A (figs. 5 to 8) there was a falling pulse-rate throughout most of the observations after the giving of the sodium-chloride solution, the rate in each case being materially lower (usually about 10 beats) in the hour or two after the injection began than in the preliminary hour previous to the injection. In three of the experiments with the mask and continuous measurements, this fall was not very marked or was practically absent, although there were variations from period to period. In the fourth experiment with the mask (March 20), there was a marked fall, but the indications are that the subject had quite recently partaken of a large meal which was sufficient to influence the metabolism at the beginning of the experiment, with a gradual lessening of this effect as the experiment progressed.

In the three mouthpiece experiments with subject C there was no marked change in the pulse-rate in the first (that of October 16), while in the other two there was a very slight fall in the second and third hours after the injection began. In the two continuous measurement experiments (with mask) on February 21 and March 16 with subject C, the pulse-rate fell markedly when the subject was asleep before the injection, but rose when he awoke. The pulse-rate after the injection was, on the whole, somewhat higher than the rate before the solution was given. This change was, in all probability, due to the change in degree of wakefulness rather than to the solution of sodium chloride.

Subject D on April 14 had a high initial pulse-rate of over 90 beats per minute. It then fell during a period of sleep and subsequently rose. There was no general change in the course of the pulse-rate after the injection took place.

In general, in this series there was a tendency when the subject was awake during the entire evening for the pulse-rate to fall slightly after the injection began, but when he slept for a short period in the first part of the experiment and awoke before the injection was given, the pulse-rate tended to remain unaltered after the injection. The fall in pulse-rate indicates a negative effect in respect to the rectal injection of sodium-chloride solution and may be taken as the natural course of the pulse-rate due to the gradual lowering of physiological processes under the conditions of rest in the early hours of evening. During measurements of the respiratory exchange of a fasting man, Benedict [1] found the pulse-rate generally slightly higher (1 to 6 beats) in the early evening ($7^h\ 00^m$ to $7^h\ 45^m$ p. m.) than for the same condition in the morning ($8^h\ 30^m$ to $9^h\ 30^m$ a. m.). If the subject has a short period of sleep and then awakes, he has recuperated sufficiently for the physiological processes to be on a higher plane of activity.

### Oxygen Absorption.

A marked variation was found in the oxygen absorption of subject A in the mouthpiece experiments, with a fall in the absorption in the second hour after the rectal injection began. In the four experiments with the mask and continuous measurements, there was likewise considerable variation.

[1] Benedict: Carnegie Inst. Wash. Pub. No. 203, 1915, p. 114.

In the experiments on December 8 and 20, the oxygen consumption did not change materially for 2 to 2½ hours following the beginning of the injection; on December 8 there was a decided fall at the end of the third hour. On March 14, the oxygen consumption very gradually decreased from the beginning of the experiment until the end of the observations, with a total fall after the beginning of the injection of about 25 c. c. The results obtained on March 20 are doubtful, because apparently the whole general level was somewhat higher than usual, and the decrease was marked during the experiment, this being presumably due to the preceding diet.

With subject C, the oxygen absorption in the three experiments with the mouthpiece likewise varied, but the variations were not of so great a magnitude as those found with subject A. There was no particular change in the general level of the oxygen consumption which may be considered a result of the rectal injection of the sodium-chloride solution. In the mask experiment with C on February 21 the oxygen consumption was materially lower at the end of the second hour after the injection than in the first hour or in the preliminary period, while in the experiment on March 16, there was no particular change after the injection during the time of the measurements. The general level after the injection was, however, slightly higher than in the preliminary period, but this can be explained by the fact that during this period the subject was asleep for a short time.

In the one experiment with subject D there were slight variations from period to period, but these were not so marked as with the preceding subjects, and the oxygen consumption did not change materially during the course of the observations.

In general, there was in this series of experiments a tendency for the oxygen absorption to fall off during the several hours of the evening experiment, more particularly in the latter part of the observations, or the oxygen consumption remained unaltered, but there was no general change in this factor which may be ascribed logically to the rectal injection of the sodium-chloride solution.

### Respiratory Quotient.

Theoretically, the injection of a solution of sodium chloride into the rectum should produce no alteration in the course of the respiratory quotient, and it should continue at the level usual in a series of periods 5 to 10 hours after a light meal. From past experience in observations of the respiratory quotient in half-hour periods, it would be expected that normally there would be slight, if any, change in the course of 2 to 4 hours with successive measurements.

A notable feature in the mouthpiece experiments with subject A is the extraordinarily wide variation in the respiratory quotient from period to period which occurred both in the preliminary measurements and in the periods subsequent to the injection of the solution. Part of this variation was undoubtedly due to varying conditions of drowsiness, as well as to the natural inconstancy of the subject himself. No effect of the injection upon the course of the quotient was apparent in three of the four experiments. In the remaining experiment there was a tendency for the quotient to fall in the second hour after injection.

The four experiments with subject A in which the measurements were

made continuously also exhibit variability in the respiratory quotient from period to period. Accordingly, it must be taken for granted that the variation in the mouthpiece experiments was not due to the pumping-out of the carbon dioxide and then a subsequent recovery in the interval when there were no measurements, but that it was a true variability and occurred regardless of whether the measurements were made continuously or at intervals. In spite of this variability, however, the four continuous measurements in the experiments with the mask indicated no general alteration in the level of the respiratory quotient subsequent to the injection of the sodium-chloride solution. Consequently, the conclusion may be drawn that the injection of a sodium-chloride solution with subject A did not *per se* produce a change in the respiratory quotient, and such changes as occurred were those which would normally take place in the course of several hours.

With subject C there were five experiments, in three of which the mouthpiece was used and the measurements were made at intervals. While the variability in the respiratory quotient from period to period was not quite so great as with subject A, the group of experiments as a whole indicated a slight lowering of the respiratory quotient during the several hours of the experiment; that is, in the second or third hour after the rectal injection, the quotient was lower than in the hour preceding the injection.

The two experiments with C in which continuous measurements were made are complicated by a period of sleep of nearly 30 minutes during the preliminary observations, which occasioned a marked depression in the respiratory quotient. When the subject awoke, the quotient rose immediately, but after the injection was given it did not undergo marked alteration during a period of 2 hours. We have, therefore, two different groups of evidence regarding the effect of the injection of a sodium-chloride solution upon the respiratory quotient. In the first group there was a slight fall which was, in all probability, due to a lowering of the metabolism and a tendency towards fatigue and drowsiness at the end of the period; in the other, with sleep in the preliminary periods, the subsequent measurements showed no alteration in the quotient.

In the one experiment with subject D, continuous measurements were made. A period of sleep during the preliminary hour resulted in a marked depression of the respiratory quotient with a subsequent rise to above the initial level after the injection was given and practical constancy thereafter for a period of nearly 2½ hours.

The course of the respiratory quotient as measured in these experiments during the evening hours has possibly a tendency towards a slight fall, particularly after a period of 2 or 3 hours; this fall was not due to the injection of the sodium-chloride solution, but rather to a natural drowsiness or fatigue occurring at the end of the day. In experiments in which the subject was asleep for most of the time, or when there was a period of sleep followed by wakefulness, the quotient was not lowered. It is evident that the conditions under which these experiments were carried out were not ideal for the study of such a fine point as the slight alterations in the respiratory quotient. Subjects should be chosen who have low deviations in results and who are able to maintain a uniform degree of wakefulness. It would be better, also, to have the experiments in the morning, rather than in the evening.

At the time this research was begun, the afternoon hours were chosen for carrying out the experiments, with no thought that the time of day might affect the constancy of the metabolism, and it was believed that with trained subjects it would be possible to secure the same results as would be secured if the observations were made in the morning hours. After the experiments had been completed, it was realized that there was not the same degree of uniformity at this period of the day as in the early morning hours. One result of the observations as a whole has been, therefore, to show that, in all likelihood, when the individual is somewhat fatigued or has reached the end of a day's work, the metabolism and the physiological functions are not so stable as after an ordinary night's rest. This is a subject which needs further investigation.

GENERAL CONCLUSIONS AND DISCUSSION OF COMPOSITE CHART.

These experiments with rectal injection of sodium-chloride solution may be looked upon as negative in their results so far as any effect of the solution itself or the method of its administration are concerned, and therefore they may be taken as controls to indicate the general trend of the pulse-rate, oxygen absorption, and respiratory quotient of these three subjects. While

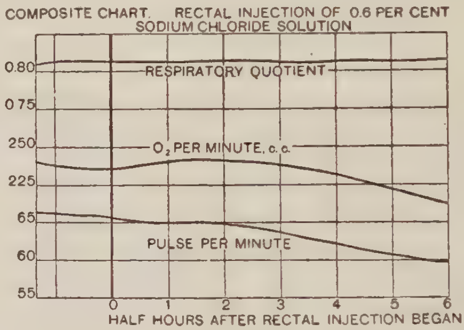



FIG. 19.—Chart showing composite results for measurements of respiratory quotient, oxygen absorption, and pulse-rate in 14 experiments with rectal injection of a 0.6 per cent solution of sodium chloride. (Mouthpiece or mask.)

they are not "basal", they will, however, serve as a basis of comparison for the effect of rectal injection of alcohol in varying concentrations and amounts, and of dextrose and levulose solutions. The comparison will not be made by subtracting these values from the values obtained in the other experiments, but by comparing the trend in the alcohol, dextrose, and levulose experiments with the trend in the experiments with the sodium-chloride solution, and by comparing the several portions of the experiments with each other and with the values obtained previous to the rectal injection.

A composite chart has been made of all the sodium-chloride experiments in which either the mouthpiece or the mask was used and is given in figure 19. This has been prepared by first making a tracing of all the charts on a sheet of transparent paper, and then the composite was drawn freehand as an estimated average of all the experiments.

*Pulse-rate.*—The average pulse-rate is shown in the chart for 40 minutes before injection and for 3 hours after injection. The pulse-rate before injection had a composite average of slightly over 66 beats per minute. This fell slightly during the first hour after injection. During the second and third hours there was a material depression in the pulse-rate to an average of 60 beats per minute at the end of the third hour. The general course of the

pulse-rate was therefore gradually downward throughout the entire period of observation.

*Oxygen absorption.*—The oxygen absorption was practically constant at a level of about 235 c. c. per minute before injection. After injection, the average rose slightly but began to fall in about $1\frac{1}{2}$ hours after injection. The final average at the end of 3 hours approximated 213 c. c. per minute, which is considerably below the initial level before the injection. For much of its course the oxygen curve practically parallels the curve for the pulse-rate. This finding is of importance in connection with the general question of the parallelism between the pulse-rate and the oxygen absorption which has been brought out in many publications from the Nutrition Laboratory.

*Respiratory quotient.*—The respiratory quotient is of importance as an indication of the degree of utilization of the material injected. Theoretically, the injection of a sodium-chloride solution should produce no change in the respiratory quotient. The average respiratory quotient in this series of experiments was practically unchanged throughout the entire experimental period of 3 hours and 40 minutes. This conclusion differs slightly from that drawn on page 95, which was based more particularly on selected experiments rather than on the group as a whole. It must be noted that this composite chart includes all of the experiments, regardless of whether the subject was asleep a portion or all of the time, or whether he was asleep in the early part of the observations and awake later. In general, the average of all the respiratory quotients during the experimental periods does not change.

## Sodium-Chloride Experiments with the Clinical Respiration Chamber.

In the winter of 1916–17, a few control experiments were carried out with subject A which continued for the entire night. In these the clinical respiration chamber[1] was used for determining the respiratory exchange. The general procedure was practically the same as that used with the breathing appliance and gasometer method. The subject usually had a substantial meal at noon, but no food afterwards. In all but the first experiment, tests connected with another research were made with him in the early part of the evening.[2] Before the measurement of the respiratory exchange he took an enema to cleanse the rectum and the large intestine, and after removing all clothing but his underwear, he lay down on a woven-wire bed-spring in the chamber. The catheter for the introduction of the solution was then inserted. This catheter was connected to the feeding reservoir by means of a capillary U-tube placed in the water-seal of the respiration chamber; it was thus possible to introduce the solution at any time after the cover of the apparatus had been put in place. Two pneumographs and a stethoscope were attached to the subject as in the breathing-appliance experiments. In the last three experiments in the series, standard electro-cardiograms were secured, and for this purpose cheese-cloth electrodes, saturated in a solution of sodium chloride, were wrapped around his left ankle and both wrists and connected to a string galvanometer.[3] After the subject had been covered

[1] Benedict and Tompkins: Boston Med. and Surg. Journ., 1916, 174, pp. 857, 898, and 939.
[2] Miles: Carnegie Inst. Wash. Pub. No. 333, 1924, pp. 111–124.
[3] For a detailed description of the electrodes and the standard electro-cardiograms obtained, see Miles: Carnegie Inst. Wash. Pub. No. 333, 1924, pp. 119–124.

with two blankets, he was ready for the observations of the respiratory exchange. In spite of the various attachments and the confinement of the chamber, the man was able to turn from side to side and to sleep the greater part of the night.

After the preliminary preparations had been completed, the cover of the apparatus was put in place, the circulation of the air was started, and observations were begun as soon as equilibrium conditions were obtained inside the chamber. Usually three periods of approximately one-half hour each were completed before the introduction of the solution began. The experiment was then continued throughout the night with periods of about equal length. Some of the clinical-chamber experiments were preceded and followed by a few periods with the breathing-appliance (mask) apparatus.

These observations with the clinical respiration chamber are discussed here in much the same manner as those made by the breathing-appliance and gasometer method. There were four experiments in all, one with distilled water, two with a 0.6 per cent solution of sodium chloride, and one with no rectal injection. A list of the experiments is given in table 22, and the results

Table 22.—*Control experiments with subject A in a clinical respiration chamber with rectal injection.*

| Date. | Solution injected. | | Duration of injection. | Periods before injection. | | Periods after injection. | |
|---|---|---|---|---|---|---|---|
| | Volume. | Weight NaCl. | | No. | Time covered. | No. | Time covered. |
| 1917. | *c. c.* | *grams.* | *min.* | | *h. min.* | | *h. min.* |
| Jan. 13–14 .. | 500 | 0 | 30 | 3 | 1 41 | 9 | 6 1 |
| Feb. 9–10 .. | 500 | 3.0 | .. | 3 | 1 34 | 10 | 5 28 |
| Mar. 16–17 .. | 0 | 0 | .. | 0 | 0 0 | 14 | 7 1 |
| Apr. 2– 3 .. | 500 | 3.0 | 76 | 2 | 1 26 | 8 | 6 2 |

are presented in the form of curves in figures 20 to 23. The chamber respiration experiments were conducted primarily as controls for the experiments with subject A, in which a 7.5 per cent alcohol solution was injected, and the measurements were continued throughout the night. The mask and gasometer experiments at the beginning or end of the chamber observations were made more especially to secure information as to conditions at the beginning and end of the main experiment, and not primarily for the study of differences in the metabolism and pulse-rate with the subject asleep and awake. And yet they do contribute to this problem, as in many cases the subject was awake in the morning.

### Pulse-Rate.

In three out of four of the chamber respiration experiments, the pulse-rate maintained a fairly constant level from beginning to end. On March 16–17 there was a marked fall at the very end, while in the experiment on April 2–3 there was a difference of 5 beats between the first and second periods before the injection took place and when the subject was in the respiration chamber. In the experiment on January 13–14, for some unknown reason the

pulse-rate was somewhat higher in the last $2\frac{1}{2}$ hours of the experiment than in the previous periods. The highest pulse-rate, however, was only 65 beats, which, for this subject, is not a very high rate. The experiments as a whole do not indicate any particular period of time when there was an absolute

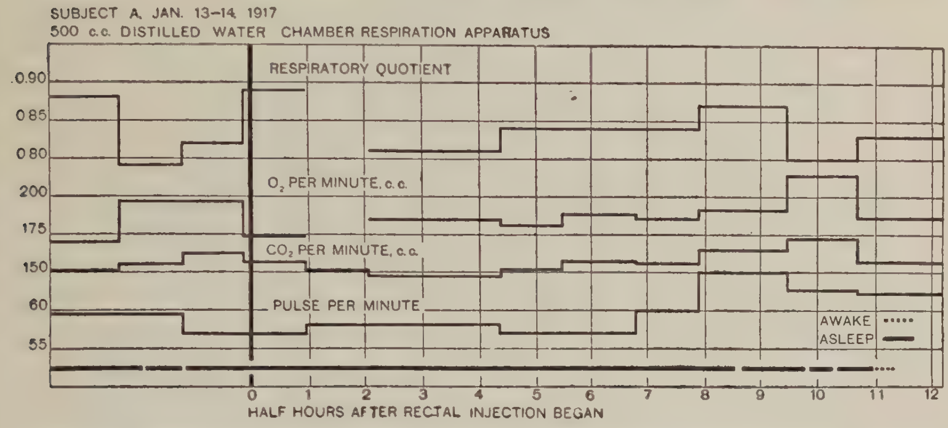



Fig. 20.—Respiratory quotient, oxygen absorption, carbon-dioxide elimination, and pulse-rate of subject A, January 13–14, 1917, before and after rectal injection of 500 c. c. of distilled water. (Chamber respiration apparatus.)

The horizontal line at the bottom of this and subsequent charts gives a record of sleep, the solid portions indicating when the subject was asleep, and the broken portions when he was awake.

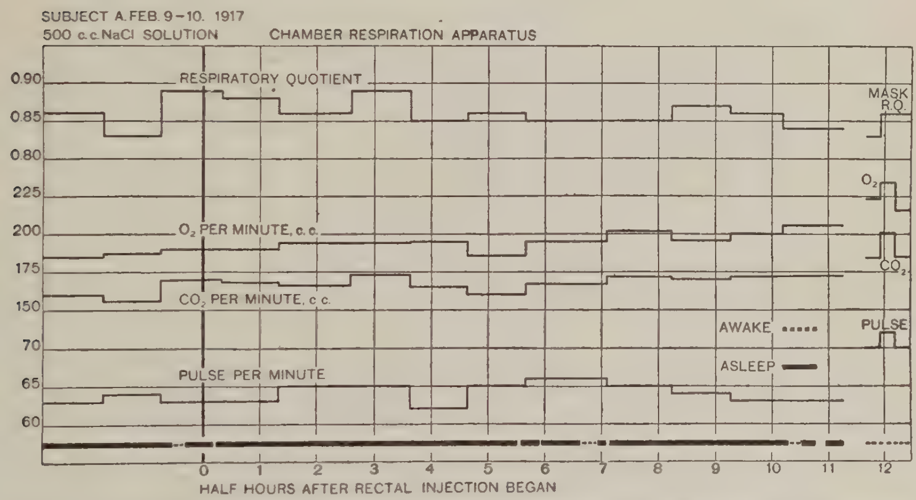



Fig. 21.—Respiratory quotient, oxygen absorption, carbon-dioxide elimination, and pulse-rate of subject A, February 9–10, 1917, before and after rectal injection of 500 c. c. of a 0.6 per cent solution of sodium chloride. (Chamber respiration apparatus, followed by observations with mask and gasometer apparatus.)

minimum for the night. In the three cases in which measurements were made with a mask and gasometer after the experiment with the chamber was concluded, the pulse-rate was materially higher, but at this time the subject was awake during practically the entire observation.

The general level of the pulse-rate for the first experiment was slightly lower than the subject's basal pulse-rate (64 beats per minute), while that for the experiment of February 9–10 was very nearly basal. The level on March 16–17 was about 5 beats higher than the basal rate, while the pulse-

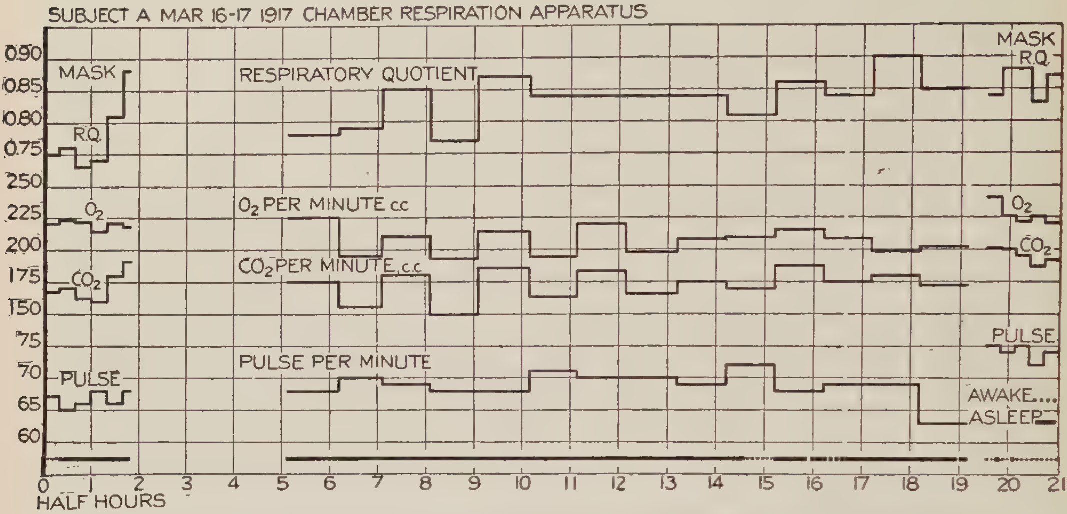



FIG. 22.—Respiratory quotient, oxygen absorption, carbon-dioxide elimination, and pulse-rate of subject A, March 16–17, 1917, with no rectal injection. (Chamber respiration apparatus, preceded and followed by observations with mask and gasometer apparatus.)

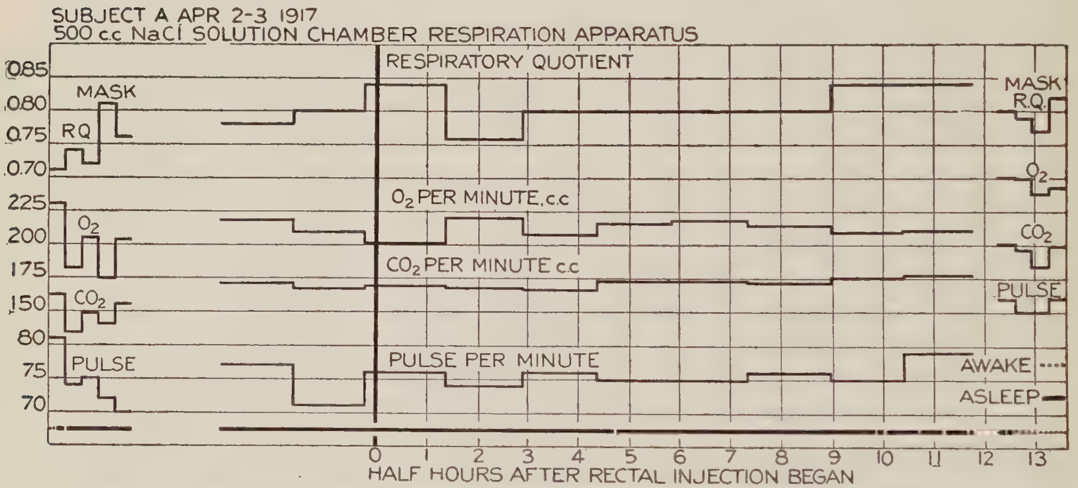



FIG. 23.—Respiratory quotient, oxygen absorption, carbon-dioxide elimination, and pulse-rate of subject A, April 2–3, 1917, with rectal injection of 500 c. c. of a 0.6 per cent solution of sodium chloride. (Chamber respiration apparatus, preceded and followed by observations with mask and gasometer apparatus.)

level of 75 beats on April 2–3 was distinctly higher (11 beats) than the basal pulse-rate.

As the subject was awake in the three morning experiments with the mask and gasometer and asleep in the chamber experiments just previous to these,

they give information as to the change in pulse-rate which took place with this change from asleep to awake. On February 10 the increase in rate per minute was 7 beats (from 64 to 71 beats); on March 17 the increase was 11 beats (from 63 to 74 beats); on April 3 the increase was 7 beats (from 79 to 86 beats). It is seen from these results that this subject, when awake immediately after a night's sleep, showed a marked increase in the heart-rate of 7 to 11 beats.

### Carbon-Dioxide Elimination.

The carbon-dioxide elimination is included in the charts for this series for the reason that with this apparatus its changes may be measured more accurately than those of the oxygen absorption, and it gives a better indication of the real trend of the total metabolism, as well as of the respiratory quotient, provided the oxygen absorption does not alter. In three of the four experiments the carbon-dioxide elimination had a slight tendency to rise. This is most marked in the experiments of January 13–14 and February 9–10, while somewhat the same tendency is apparent in the chart for the experiment of March 16–17. For some unexplainable reason, the carbon-dioxide elimination in the experiment of March 16–17 shows a type of alternation which would not be expected under these conditions. This tendency for the carbon-dioxide elimination to rise confirms the same tendency found with the respiratory quotient. The values for the carbon dioxide measured in short periods after the chamber experiment was over are always somewhat higher than those determined with the chamber apparatus, but again it must be recalled that the subject was usually awake in these periods, while in the chamber he was asleep.

From the values given in the charts, a comparison may be made of the carbon-dioxide production with the subject asleep and awake. The increases are: February 10, 18 c. c. (from 172 to 190 c. c.); March 17, 21 c. c. (from 174 to 195 c. c.); and April 3, 20 c. c. (from 175 to 195 c. c.). As the respiratory quotients are practically the same for both conditions in the morning, these increases show the metabolic increase in the change from asleep to awake, i. e., about 11 per cent.

### Oxygen Absorption.

The oxygen absorption is liable to show variable figures in experiments with the clinical respiration chamber because of the difficulty in measuring the average temperature at the end of each period. In two of these experiments, however (January 13–14 and February 9–10), there is a general tendency toward a slight rise in this factor, the values on February 9–10 being the most consistent of any in the four experiments. The other two experiments exhibit no tendency toward a change in either direction. As with the carbon-dioxide elimination, the values obtained in the morning with the gasometer and mask are materially higher than those obtained during the night with the chamber apparatus. The increases in the oxygen consumption when the subject awoke in the morning were as follows: February 10, 23 c. c. (from 201 to 224 c. c.); March 17, 19 c. c. (208 to 227 c. c.); and April 3, 30 c. c. (215 to 245 c. c.). The average increase was 24 c. c. per minute, i. e., slightly over 11 per cent. The increase in the oxygen consumption of this subject in the morning change from asleep to awake was thus of the same order as the change in the carbon-dioxide production.

RESPIRATORY QUOTIENT.

The respiratory quotient did not change very materially in one direction or the other, although it varied from period to period. These variations, however, probably do not represent true changes in the respiratory quotient, but rather indicate the difficulty of measuring quotients with the chamber apparatus in short periods. The least variation is found in the experiment on February 9–10, in which slight or no change occurred in the respiratory quotient from the beginning of the experiment until the end. A measurement with the gasometer and mask combination is in accord with the quotient obtained in the morning. In three of the experiments there was a slight tendency for the quotient to rise during the night. This is shown most markedly in the experiment of March 16–17, and the end-quotients confirm those obtained with the gasometer and mask. The same change may be seen in the experiment of April 2–3, though not to so marked a degree, and there is a slight tendency towards a rise in the experiment of January 13–14.

A change in the quotient between the evening and morning has already been found in a series of experiments with a fasting man[1] whose metabolism was measured by the universal respiration apparatus in the evening before he went into the chamber of the respiration calorimeter, in which he spent the night, and again in the morning immediately after he left the chamber. In every case, the morning respiratory quotient of this fasting man was slightly higher (0.01 to 0.05) than the evening respiratory quotient obtained under the same conditions of measurement. The interpretation given was that this lowering of quotient in the evening experiments might be taken as an indication either that there was a formation from fat of carbohydrate which in the morning was burned, or that there was a greater formation of $\beta$-oxybutyric acid in the evening than in the morning. Benedict did not consider it justifiable to lay much stress on the differences in quotient, but it is evident from the experiments with subject A that the differences with the fasting man were really of significance.

It is evident from the experiments reported in this monograph that the process, whatever it is, is a very gradual one and that the increase is not large. One may suppose that at the end of the waking period the readily available supply of high quotient material (carbohydrate) has reached its minimum and that the condition of minimum activity during sleep brings about a condition in which this material can be formed more rapidly than it is utilized. As a result, there is a gradual increase in availability and in consequence a greater utilization of the high quotient material in metabolism. Whether it is carbohydrate formation from fat, a gradual decrease in partially oxidized products, or a gradually increasing availability of the carbohydrate portion of protein can not be stated from these experiments.

Experiments are needed to determine more exactly the rate and amount of the increase in the respiratory quotient during a night's sleep and the nutritive conditions which govern it. From the experiments by Benedict on the fasting man and the series here reported, it is evident that the increase in the respiratory quotient as the result of long periods of sleep is a real change in metabolism.

[1] Benedict: Carnegie Inst. Wash. Pub. No. 203, 1915, p. 334, table 46; also p. 338.

### GENERAL CONCLUSIONS REGARDING EXPERIMENTS WITH CLINICAL RESPIRATION CHAMBER.

In general, it may be said that in the control experiments made during the night, the pulse-rate remained practically unaltered, except as it was affected by variations in wakefulness; that the carbon-dioxide elimination rose slightly; that the oxygen absorption rose very slightly or remained unchanged as the night progressed; and that the respiratory quotient had but a slight tendency to alter, and that this tendency was in the upward direction. The changes, therefore, are such as would presumably occur in normal night experiments and may be looked upon as contributions to the normal metabolism during sleep. In discussing the course of the metabolism and pulse-rate in the night experiments with the chamber apparatus in which a 7.5 per cent alcohol solution was given, these chamber experiments in the sodium-chloride series will be used as a basis of comparison. (See p. 120.) As the experiments in this series were few in number and dissimilar as to character of injection, no composite chart has been made for them.

## RESPIRATORY EXCHANGE WITH RECTAL INJECTION OF ALCOHOL SOLUTIONS.

As has previously been brought out, this investigation was begun primarily as a study upon the effect of the rectal injection of alcohol solutions, the sodium-chloride experiments being made simply as controls. The method of conducting the alcohol experiments was the same as for the control experiments. The concentrations of the ethyl alcohol in the solutions used were 5, 7.5, and 10 per cent by weight in distilled water. The solution was made up from a concentrated alcohol whose strength had been estimated from density values determined with a Squibb 50-c. c. pyknometer. In the discussion of the results, the experiments are grouped, first, according to the percentage of alcohol in the solution; second, according to the volume of the solution injected; and third, according to subjects.

### Experiments with a 5 per cent Alcohol Solution.

The first group of observations with alcohol injection was made with a 5 per cent solution of alcohol. Table 23 shows the number and character of the experiments grouped according to volume and subject. These experiments were carried out with the same individuals and in the same manner and under the same conditions, except for the solution injected, as the experiments with the sodium-chloride solution, i. e., they were usually late in the afternoon, the last food taken by the subject being in the morning. In two of the experiments the subject was post-absorptive, namely, those with A on October 12, and with C on October 24. In the other mouthpiece experiments, the last food was taken not later than $1^{h}$ $30^{m}$ p. m., and usually before 9 a. m. The experiments generally began about $5^{h}$ $30^{m}$ p. m.

The volume injected varied from 220 c. c. to 1,020 c. c. Using round numbers, there were 2 experiments with 200 c. c., 6 with 300 c. c., 4 with 400 c. c., 3 with 500 c. c., and 1 with 1,020 c. c. The time of injection was not recorded in all of the experiments, but such records as are available vary from 1 to 68 minutes, except in the experiment of April 17, when it was 270 minutes. In all but one experiment, observations preceded the giving of the alcohol, the number of periods before injection ranging from 1 to 8, and the

length of period from 4 to 15 minutes. The total period of time covered ranged from 4 minutes to 1 hour and 14 minutes. The number of periods after injection varied from 9 to 26, and the time covered from 1 hour and 58 minutes to 6 hours and 11 minutes. In the discussion, the observations before the injection are first considered and then the data obtained during and subsequent to the injection. In discussing the latter, the experiments are grouped according to the volume of the injection, i. e., approximately 200, 300, 400, and 500 to 1,000 c. c., with a general summary of the effect of the alcohol. The results of the observations are given graphically in figures 24 to 39.

TABLE 23.—*Statistics of respiratory exchange observations before and after the injection by rectum of a 5 per cent alcohol solution.*

| Subject. | Date.[a] | Alcohol injected. | | Duration of injection. | Periods before injection. | | Periods after injection. | |
|---|---|---|---|---|---|---|---|---|
| | | Volume of solution. | Weight of alcohol. | | No. | Time covered. | No. | Time covered. |
| | 1915. | *c. c.* | *gm.* | *min.* | | *h. min.* | | *h. min.* |
| A | Oct. 5 | 220 | 11 | 1 | 3 | 0 40 | 11 | 3 28 |
| | Oct. 8 | 220 | 11 | 10 | 3 | 0 36 | 11 | 3 19 |
| | Oct. 12[b] | 320 | 16 | 11 | 3 | 0 36 | 17 | 5 6 |
| | Oct. 27 | 300 | 15 | . . | 5 | 1 0 | 9 | 2 49 |
| | Nov. 10 | 320 | 16 | 25 | 3 | 0 32 | 15 | 3 18 |
| C | Oct. 24[b] | 325 | 16.3 | 5 | 5 | 1 3 | 12 | 2 37 |
| | Oct. 29 | 320 | 16 | 3 | 1 | 0 4 | 15 | 3 46 |
| | Nov. 8 | 320 | 16 | . . | 4 | 0 35 | 15 | 3 24 |
| A | Nov. 18 | 400 | 20 | 11 | 4 | 0 54 | 10 | 1 58 |
| | Nov. 24 | 420 | 21 | 13 | 8 | 1 14 | 17 | 2 30 |
| | Dec. 2 | 420 | 21 | . . | 7 | 1 6 | 21 | 3 11 |
| C | Nov. 29 | 420 | 21 | 33 | 6 | 1 1 | 18 | 2 28 |
| | 1916. | | | | | | | |
| A | Apr. 3 | 510 | 25.5 | 68 | 0 | 0 0 | 23 | 3 59 |
| D | Feb. 18 | 520 | 26 | 33 | 6 | 1 0 | 20 | 3 20 |
| | Feb. 25 | 510 | 25.5 | 47 | 7 | 1 5 | 20 | 2 54 |
| A | Apr. 17 | 1,020 | 51 | 270 | 3 | 0 36 | 26 | 6 11 |

[a] Previous to the experiment of Nov. 18, 1915, with A, the mouthpiece was used, but on Nov. 18 and thereafter the mask was employed. With the mouthpiece, the subject was in the sitting position, except on Oct. 5, 1915, when he lay down; with the mask, he lay on a couch, except on Nov. 29, 1915, when he sat in a chair.

[b] Subject in a post-absorptive condition.

## RESULTS OF MEASUREMENTS BEFORE RECTAL INJECTION.

In those experiments in which the mouthpiece was used, there was a half-hour rest before the first period, while in the experiments with the mask the measurements began as soon as the subject lay down. In the charts of the mask experiments only the three or four periods immediately before the injection are included, although usually, as may be seen from table 23, six or more periods preceded the injection. The first observation indicated on each curve for the mask experiments was thus nearly a half hour after the subject lay down. The men showed the same degree of variability in all measurements which was found with the sodium-chloride solution. This was particularly true of subject A, while subject C was more nearly uniform in the measurements from period to period. These measurements were made under

conditions which are strictly comparable with the measurements made in the pre-injection periods of the previous group.

### Pulse-Rate.

The average pulse-rate in the preliminary periods with subject A varied from 59 beats per minute on April 17 to 79 beats per minute on October 27. When the subject came to the Laboratory on October 27, he was emotionally disturbed and was thus not in an ideal condition for an experiment of this character. The results show very clearly the influence of the disturbed psychic condition upon the pulse-rate, and likewise upon the metabolism as represented by the oxygen absorption. The pulse-rate was unusually high at the beginning of the experiment, but fell gradually during the evening. The oxygen consumption remained at a high level throughout the experiment, with but little permanent change from the preliminary values. These results illustrate the necessity for assurance that the subject is in a quiet emotional condition in order that true values may be obtained for comparison with those found in studying a superimposed factor. This is in line with the recommendation repeatedly made in publications from this Laboratory as to ideal conditions for the determination of basal metabolism. The second highest average pulse-rate before injection in the series with A was 73 beats. In the majority of the experiments with this subject, the preliminary pulse-rate was not far from that obtained under basal (post-absorptive) conditions on October 12, i. e., 64 beats per minute. Subject C varied in the preliminary period from 64 beats to 69 beats which approximated his basal pulse-rate on October 24. The pulse-rate in the two experiments with subject D averaged before injection 80 and 84 beats, respectively. This subject was characterized by a high pulse-rate in all his experiments.

### Oxygen Absorption.

With the exception of October 27, the oxygen absorption of subject A in the periods before injection varied, on the average, from 186 to 209 c. c. per minute; on October 27 the average value was 239 c. c. As brought out in the discussion of the pulse-rate, the experiment on October 27 illustrates clearly the necessity in metabolism studies of having the subject tranquil, since a disturbed mental condition may result in a disturbed metabolism. In most of the other experiments with A, the preliminary values were not far from the basal oxygen consumption obtained on October 12, which was 209 c. c.

With subject C the oxygen absorption varied on the average before injection from 278 to 291 c. c. per minute; the basal (post-absorptive) value on October 24 was 280 c. c. The range in oxygen absorption in the preliminary periods of this series of experiments with subject C was narrower than that in the experiments with the sodium-chloride solution.

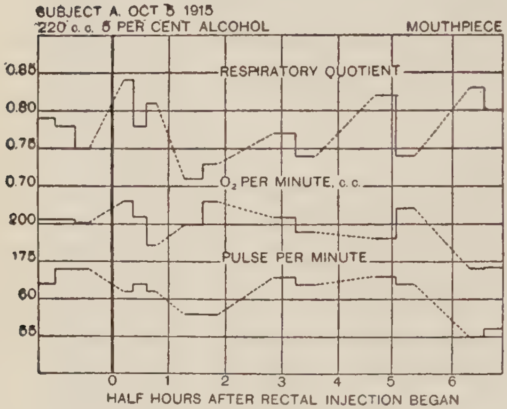
With subject D the average values for the preliminary periods in the two experiments are 224 c. c. and 231 c. c. per minute, which was lower than the oxygen absorption (250 c. c.) in the one experiment with the sodium chloride. We have no basal experiment with this subject.

### Respiratory Quotient.

With subject A on November 24 and December 2, the average values before injection are rather high, namely, 0.86 and 0.88. The last food taken before the experiments on these days was at 8 and 10 a. m., respectively.

We see no cause for these high respiratory quotients previous to injection. The other preliminary values for this subject range from 0.76 to 0.82.

With subject C the quotients ranged before injection from 0.84 to 0.77. With subject D they averaged 0.81 and 0.78. With the exception of 0.76,

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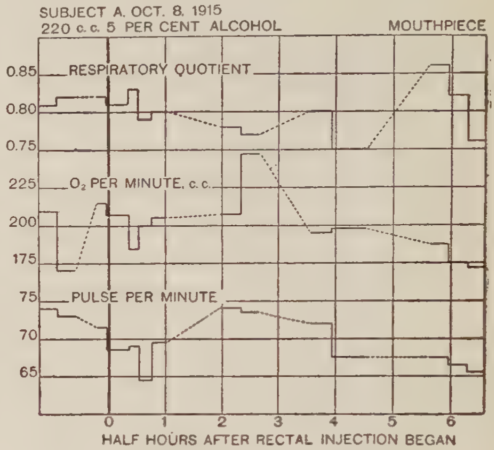


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Fig. 24—Respiratory quotient, oxygen absorption, and pulse-rate of subject A, October 5, 1915, before and after rectal injection of 220 c. c. of a 5 per cent alcohol solution. (Mouthpiece, with intermittent observation.)

The solid portions of the three curves represent the averages for the periods, and the broken portions the intervals between observations. This applies to all subsequent experiments with the mouthpiece.

Fig. 25.—Respiratory quotient, oxygen absorption, and pulse-rate of subject A, October 8, 1915, before and after rectal injection of 220 c. c. of a 5 per cent alcohol solution. (Mouthpiece, with intermittent observation.)

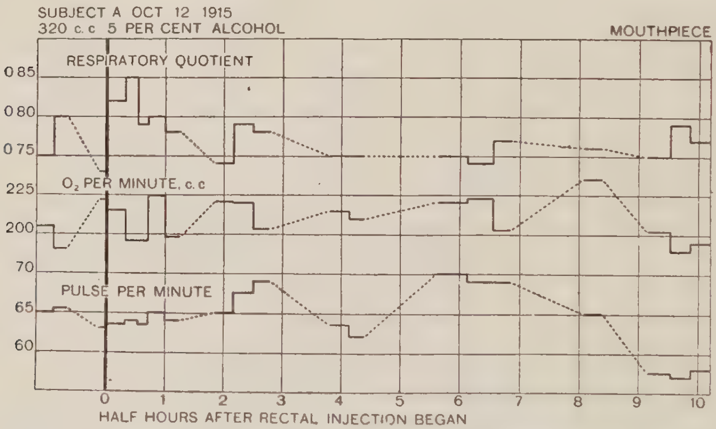
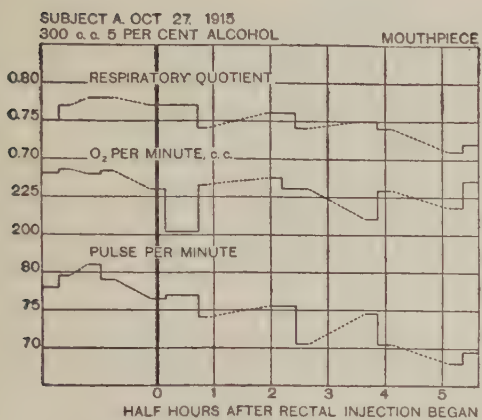



Fig. 26.—Respiratory quotient, oxygen absorption, and pulse-rate of subject A, October 12, 1915, before and after rectal injection of 320 c. c. of a 5 per cent alcohol solution. (Mouthpiece, with intermittent observation.)

0.77, and 0.78 noted above, the respiratory quotients for the periods preceding injection in this series with a 5 per cent alcohol solution are very near the normal values for a post-absorptive or basal condition. While some quotients are slightly lower than would be expected, it is seen from the experi-

ments with the sodium-chloride solution that the respiratory quotient in the evening tends to be low, with a gradual *increase* throughout the whole night, and it is quite likely that the conditions were the same in this respect in both series.

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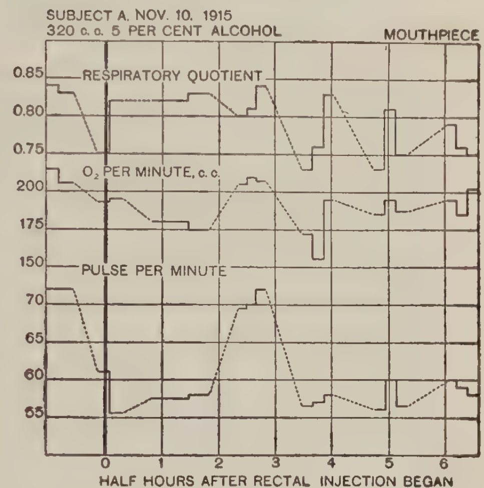


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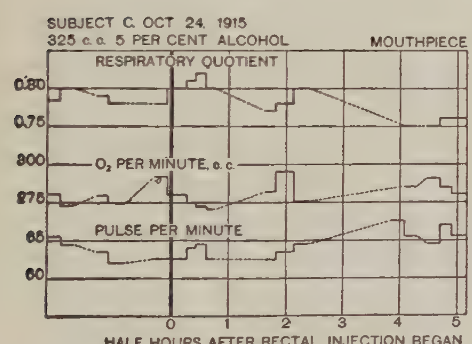
FIG. 27.—Respiratory quotient, oxygen absorption, and pulse-rate of subject A, October 27, 1915, before and after rectal injection of 300 c. c. of a 5 per cent alcohol solution. (Mouthpiece, with intermittent observation.)

FIG. 28.—Respiratory quotient, oxygen absorption, and pulse-rate of subject A, November 10, 1915, before and after rectal injection of 320 c. c. of a 5 per cent alcohol solution. (Mouthpiece, with intermittent observation.)

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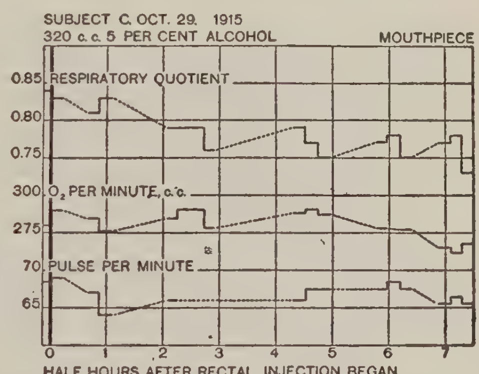


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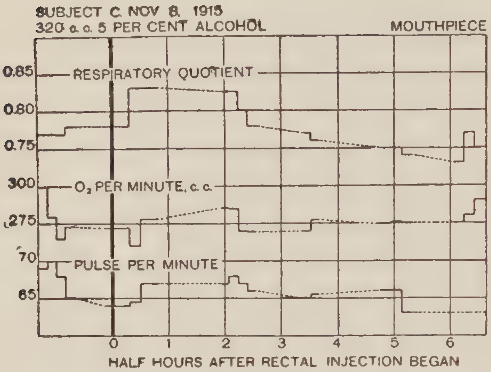
FIG. 29.—Respiratory quotient, oxygen absorption, and pulse-rate of subject C, October 24, 1915, before and after rectal injection of 325 c. c. of a 5 per cent alcohol solution. (Mouthpiece, with intermittent observation.)

FIG. 30.—Respiratory quotient, oxygen absorption, and pulse-rate of subject C, October 29, 1915, before and after rectal injection of 320 c. c. of a 5 per cent alcohol solution. (Mouthpiece, with intermittent observation.)

## RESULTS OF MEASUREMENTS AFTER RECTAL INJECTION OF A 5 PER CENT ALCOHOL SOLUTION.

### Experiments with 200 Cubic Centimeters.

The general course of the pulse-rate, respiratory quotient, and oxygen absorption in the two experiments with subject A was practically the same as that found when a solution of sodium chloride was injected. While there

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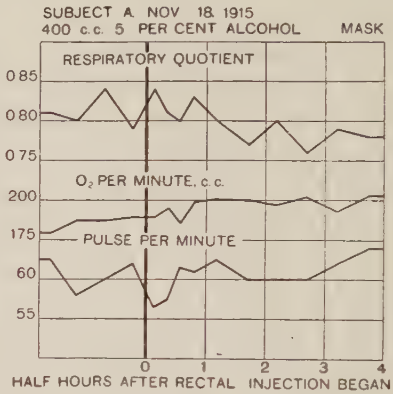


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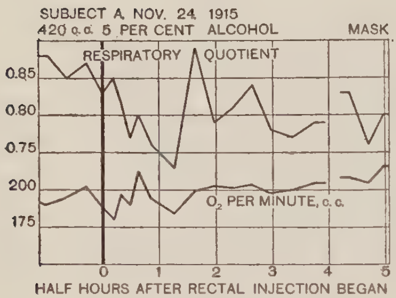
Fig. 31.—Respiratory quotient, oxygen absorption, and pulse-rate of subject C, November 8, 1915, before and after rectal injection of 320 c. c. of a 5 per cent alcohol solution. (Mouthpiece, with intermittent observation.)

Fig. 32.—Respiratory quotient, oxygen absorption, and pulse-rate of subject A, November 18, 1915, before and after rectal injection of 400 c. c. of a 5 per cent alcohol solution. (Mask, with continuous observation.)

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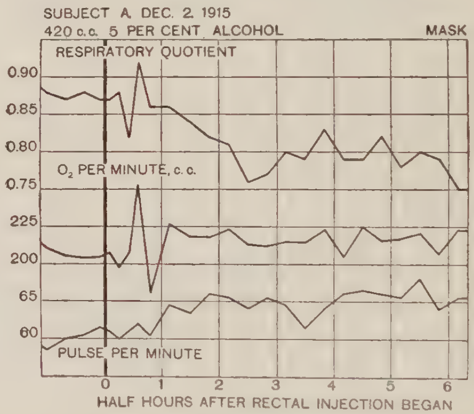


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Fig. 33.—Respiratory quotient, and oxygen absorption of subject A, November 24, 1915, before and after rectal injection of 420 c. c. of a 5 per cent alcohol solution. No pulse records made. (Mask, with continuous observation.)

Fig. 34.—Respiratory quotient, oxygen absorption, and pulse-rate of subject A, December 2, 1915, before and after rectal injection of 420 c. c. of a 5 per cent alcohol solution. (Mask, with continuous observation.)

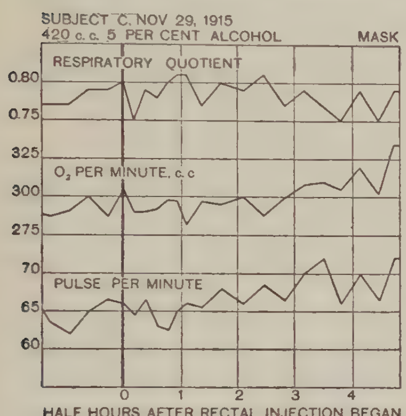
were marked variations from time to time in all the factors, these were apparently due to sleep or drowsiness rather than to the alcohol solutions. From these two experiments alone it may be stated that the injection into the rectum of 200 c. c. of a 5 per cent alcohol solution, i. e., 10 grams of

absolute ethyl alcohol, produces no change in the three factors observed, namely, respiratory quotient, oxygen absorption, and pulse-rate.

### Experiments with 300 Cubic Centimeters.

The results of a larger number of experiments with 300 c. c. of a 5 per cent alcohol solution are available for comparison, there being three each with subjects A and C.

With subject A the respiratory quotient was practically unaltered by the alcohol. The only possible exception to this was on October 12, when there was a fall, which occurred about 2 hours after the beginning of the injection, and coincided with a fall in pulse-rate. With a later high pulse-rate, however, the respiratory quotient was at a low level. The oxygen absorption

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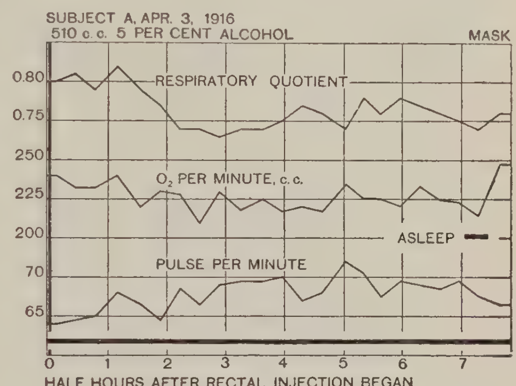


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**Fig. 35.—Respiratory quotient, oxygen absorption, and pulse-rate of subject C, November 29, 1915, before and after rectal injection of 420 c. c. of a 5 per cent alcohol solution. (Mask, with continuous observation.)**

**Fig. 36.—Respiratory quotient, oxygen absorption, and pulse-rate of subject A, April 3, 1916, after rectal injection of 510 c. c. of a 5 per cent alcohol solution. (Mask, with continuous observation.)**

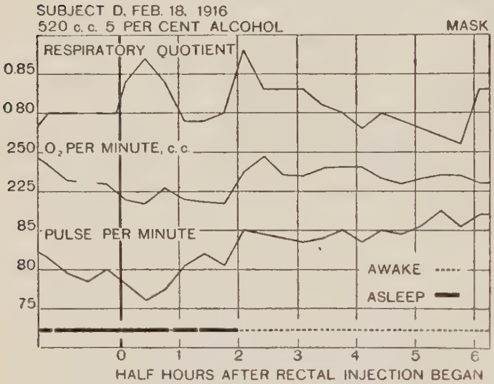
**The horizontal line at the bottom of this and subsequent charts gives a record of sleep, the solid portions indicating when the subject was asleep, and the broken portions when he was awake.**

fell off very slightly in two experiments in about the same manner as with a sodium-chloride solution. The pulse-rate fell slightly not only on October 12, but also on October 27. From the experiments with subject A, it is questionable whether the conclusion can be drawn that the injection of 15 grams of alcohol in a 5 per cent solution introduced rectally produced any specific effect, especially as the results were more or less complicated by drowsiness.

In the three experiments with subject C the oxygen absorption and pulse-rate were practically unaltered by the alcohol injection. There was a slight fall in the respiratory quotient in the three experiments, and as this fall was not accompanied by a similar lowering in pulse-rate, it was probably due to the effect of alcohol upon the metabolism. These experiments with C indicate a slight effect upon the character of the metabolism after the giving of 300 c. c. of a 5 per cent alcohol solution by rectum.

### Experiments with 400 Cubic Centimeters.

Of the four experiments with approximately 400 c. c., three were with subject A and one with subject C. On November 18 and December 2, subject A was asleep the greater part of the experiment; on November 24 there was some disquiet due to trouble with the mask. In one of the experiments with subject A, the respiratory quotient was practically unchanged. In the other two there was a fall, particularly in the experiment of December 2, one hour after the beginning of the injection. The fall in respiratory quotient was accompanied by a rise in the pulse-rate. In the experiments with the sodium-chloride solution, a fall in the respiratory quotient was usually accompanied by a fall in the pulse-rate, which was due to drowsiness. When, however, there is a fall in the respiratory quotient which logically would be expected when alcohol is burned, and, at the same time, there is a rise in the pulse-rate which has been shown by previous work to occur after alcohol has been given, we are led to the conclusion that the two changes, that is, the lowering of the respiratory quotient and the increase in the pulse-rate, are due to the taking of the alcohol.

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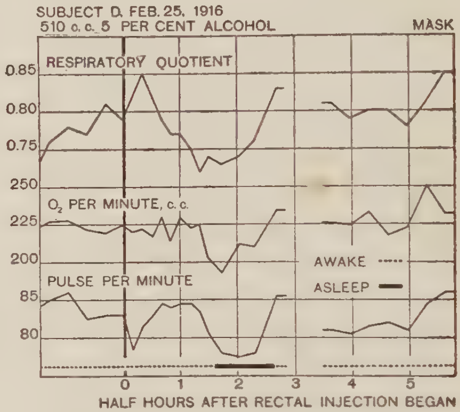


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Fig. 37.—Respiratory quotient, oxygen absorption, and pulse-rate of subject D, February 18, 1916, before and after the rectal injection of 520 c. c. of a 5 per cent alcohol solution. (Mask, with continuous observation.)

Fig. 38.—Respiratory quotient, oxygen absorption, and pulse-rate of subject D, February 25, 1916, before and after rectal injection of 510 c. c. of a 5 per cent alcohol solution. (Mask, with continuous observation.)

The oxygen consumption was actually higher in all three experiments after the injection of alcohol than before, and in all probability the rise, at least some part of it, was due to the alcohol. The change in pulse-rate on November 18, if any, was in the direction of acceleration. On December 2 there was a gradual increase in the pulse-rate from the beginning to the end of the experiment. Owing to the non-functionating of the recording apparatus no measurements could be made of the pulse-rate on November 24. We have, then, with subject A and 400 to 420 c. c. of a 5 per cent alcohol solution, two experiments (November 18 and 24) in which the influence of the alcohol was slightly noticeable, and one experiment (December 2) in which there was a consistent influence, namely, a decrease in the respiratory quotient and an increase in the pulse-rate.

The experiment with subject C with 420 c. c. of a 5 per cent alcohol solution exhibited a tendency in the same direction as those with subject A, but slight activity may have played a rôle.

### Experiments with 500 to 1,000 Cubic Centimeters.

Three experiments were made with 500 c. c. of a 5 per cent alcohol solution, one with subject A and two with subject D. In the experiment with A the subject was asleep the whole of the experimental period. After the first hour there was a marked fall in the respiratory quotient. Unfortunately, there were no preliminary periods in this experiment with which the results can be compared, but judging by other experiments in which alcohol was given by rectum, it is reasonable to assume that this fall is a positive change due to the influence of the alcohol, as its effect does not usually become apparent until after the first hour. The pulse-rate rose slightly during the experiment. The oxygen absorption fell slightly during the first $1\frac{1}{2}$ hours and was constant thereafter until the very last period.

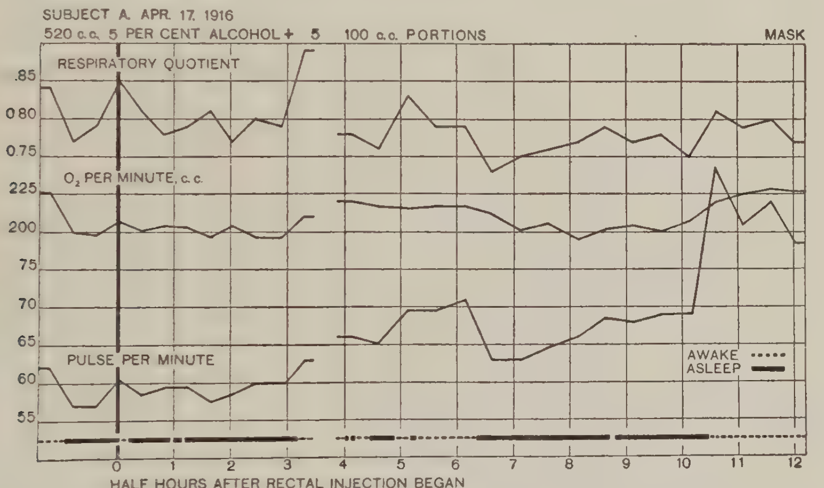



Fig. 39.—Respiratory quotient, oxygen absorption, and pulse-rate of subject A, April 17, 1916, before and after rectal injection of 520 c. c. of a 5 per cent alcohol solution, followed by five 100 c. c. portions, with a total injection of 1,020 c. c. over a period of $4\frac{1}{2}$ hours. (Mask, with continuous observation.)

In the experiments with subject D on February 18 and 25, the conditions as to sleep were very variable, which makes comparison between the results obtained before and after alcohol difficult. The subject was quiet in both experiments. The course of the respiratory quotient was very irregular and the changes are not clearly attributable to the effect of the alcohol, excepting possibly those which occurred in the last few periods of the experiment on February 18. The oxygen absorption in neither experiment was influenced by the alcohol. The pulse-rate was affected to some extent, apparently, in the experiment on February 18, but on February 25 there was no change. Here again is a condition when one experiment with a subject shows no effect and the other exhibits a specific influence on the respiratory quotient and the pulse-rate, decreasing the one and increasing the other.

There was only one experiment with 1,000 c. c. of a 5 per cent solution of alcohol. The most noticeable effect of this injection was upon the pulse-rate, which changed from a level of 58 beats before the alcohol was given to 78 beats 6 hours after the injection began. Although affected by varying amounts of sleep, the course of the pulse-rate was evidently affected by the alcohol given. The respiratory quotient fell after 2 hours and the oxygen was slightly increased.

### DISCUSSION OF COMPOSITE CHART.

In figure 40 is a composite chart for the experiments with a 5 per cent alcohol solution, which has been drawn in the same manner as the chart for the sodium-chloride experiments. As many of these alcohol experiments were of longer duration than the sodium-chloride experiments, the chart has been extended so as to represent 4 hours after the rectal injection began. The duration of the preliminary period is the same as that for the preceding series (40 minutes). All of the experiments except that with a solution of 1,020 c. c. are included in this composite. This experiment is omitted because of the larger quantity of alcohol and the long period of injection.

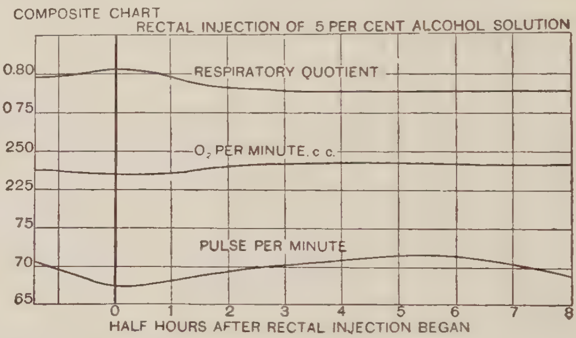



FIG. 40.—Chart showing composite results for measurements of respiratory quotient, oxygen absorption, and pulse-rate in 15 experiments with rectal injection of 11 to 26 grams of alcohol in a 5 per cent solution. (Mouthpiece or mask.)

*Pulse-rate.*—The preliminary pulse-rate in these alcohol experiments was slightly higher than that with the sodium-chloride solution, being about 71 beats at the beginning and falling to 67 beats before the injection began. It rose within the first half hour after injection and continued rising gradually for 2½ hours after injection, to a maximum of 72 beats, i. e., an increase of 5 beats over that at the end of the preliminary period. This level was maintained for some time and then the pulse-rate began to fall. Even at the end of 4 hours the rate was still higher than when the injection began. This is in contrast to the results obtained in the sodium-chloride experiments, in which the pulse-rate gradually fell. With the sodium-chloride solution, the pulse-rate was 62 beats at the end of 2 hours; with the 5 per cent alcohol solution it was 71 beats at the end of 2 hours. There was accordingly a difference in level of 9 beats. It must be noted here again that this chart includes alcohol experiments with the smaller quantities of alcohol in which there was slight, if any, influence, as well as those with larger quantities in which the influence was more marked.

*Oxygen absorption.*—The oxygen absorption in the preliminary period of this series was about the same as in the sodium-chloride experiments, namely, 237 c. c. It did not change materially until the second half hour after in-

jection, when it began to rise slightly, with a maximum increase of about 8 c. c. This level was maintained throughout the remaining 3 hours after injection. This is in contrast to the average oxygen absorption with the sodium-chloride injection, which gradually fell in the second and third hours after injection.

*Respiratory quotient.*—The respiratory quotient with the 5 per cent alcohol solution averaged about 0.80 during the preliminary period. It then fell about 0.02 during the second half hour after injection, and remained at this level for the remaining 3 hours of the experiments.

This composite chart shows, therefore, that there was a definite, though slight, influence as a result of the injection of a 5 per cent alcohol solution in quantities varying from 200 to 500 c. c. It must be noted here again that the chart includes experiments in which the amounts given were so small that the effect was slight and when superimposed upon the total values of pulse-rate, oxygen absorption, and respiratory quotient, the influence could not be detected. Because with 200 c. c. of a 5 per cent alcohol solution the effect was not clearly apparent, one must not suppose that there was no utilization of alcohol. If a subject were available who could maintain an even metabolism and an unaltered degree of wakefulness as well as of quietness, it is probable that quantities as small as 200 c. c. would show a definite utilization.

## GENERAL CONCLUSIONS REGARDING EXPERIMENTS WITH A 5 PER CENT ALCOHOL SOLUTION.

It must be admitted that the experiments in this series are hardly sufficient in number for the drawing of very definite conclusions with each quantity regarding the effect upon the pulse-rate, oxygen absorption, and respiratory quotient of the rectal introduction of a 5 per cent alcohol solution. The general statement may be made that 200 c. c. had no measurable effect upon these factors; that 300 c. c., given to two subjects, produced a slight lowering of the respiratory quotient with one of them; that 400 c. c. in 4 experiments tended to lower the respiratory quotient and raise the pulse-rate and oxygen absorption; and that 500 c. c. in 2 out of 3 experiments had the characteristic alcohol effect, fall in the respiratory quotient and rise in the pulse-rate. Solutions in quantities of 500 c. c. or under, containing 5 per cent alcohol, may cause the pulse-rate and oxygen absorption to rise slightly and the respiratory quotient to fall significantly. The one experiment with 1,000 c. c. shows a definite fall in the respiratory quotient after 2 hours. The pulse-rate began to rise in $1\frac{1}{2}$ hours, while the oxygen absorption was slightly increased at the end of 2 hours. It is surprising that the effect is not more marked with this quantity of alcohol. The general picture of this group of alcohol experiments therefore differs from that found with the sodium-chloride solution.[1]

[1] The sodium-chloride experiments were made primarily to obtain the course of the metabolism during this period of the day and also to determine whether the rectal injection of a solution, which presumably of itself has no influence upon the metabolism, would, in any way, alter its general course. Therefore, we use the results of these experiments as a contrast, or for comparison purposes, with the experiments when alcohol was taken by rectum. It was shown in the sodium-chloride experiments that the respiratory quotient either tended to remain unaltered or else it declined slightly during the evening session, but at no point was this decline sharp. The figures for oxygen absorption were inclined to remain unaltered or to be lowered slightly, while the pulse-rate showed in general a gradual decline through the evening.

### Experiments with a 7.5 per cent Alcohol Solution.

A number of experiments were carried out in which the solution used for rectal injection contained 7.5 per cent alcohol by weight. The volume of the solution varied. In three experiments 265 c. c. of a 7.5 per cent alcohol solution were used, this amount containing 19.9 grams of alcohol. One experiment was made with 350 c. c., or 26.3 grams of alcohol, and another with 415 c. c., or 31.1 grams of alcohol. In two experiments approximately 500 c. c. of a 7.5 per cent alcohol solution were given, or 37.5. grams of alcohol. In one experiment with subject C on April 18, 510 c. c. of a 7.5 per cent alcohol solution were first given and then 6 portions of 50 c. c. each of the same concentration were added, or a total amount of 810 c. c., i. e., 60.8 grams.

Table 24.—*Statistics of respiratory exchange observations before and after the injection by rectum of a 7.5 per cent alcohol solution.*

| Subject. | Date.[a] | Alcohol injected. | | Duration of injection. | Periods before injection. | | | Periods after injection. | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Volume of solution. | Weight of alcohol. | | No. | Time covered. | | No. | Time covered. | |
| | 1916. | *c. c.* | *gm.* | *min.* | | *h.* | *min.* | | *h.* | *min.* |
| A | Feb. 28 | 265 | 19.9 | 18 | 10 | 0 | 54 | 25 | 3 | 19 |
| C | Mar. 1 | 265 | 19.9 | 18 | 4 | 0 | 40 | 16 | 2 | 40 |
| D | Mar. 3 | 265 | 19.9 | 26 | 4 | 0 | 40 | 23 | 4 | 2 |
| A | Apr. 10 | 350 | 26.3 | 31 | 3 | 0 | 30 | 26 | 4 | 49 |
| C | Mar. 22 | 415 | 31.1 | 20 | 6 | 1 | 00 | 19 | 3 | 10 |
| A | Apr. 15 | 500 | 37.5 | 29 | 4 | 0 | 40 | 19 | 3 | 41 |
| C | Mar. 29 | 510 | 38.3 | (?) | 0 | 0 | 00 | 27 | 4 | 44 |
| | Apr. 18 | [b]810 | 60.8 | 286 | 2 | 0 | 26 | 24 | 5 | 33 |
| | 1917. | | | | | | | | | |
| A | Jan. 20–21 | 500 | 37.5 | 76 | 3 | 1 | 33 | 10 | 6 | 52 |
| | Feb. 3– 4 | 500 | 37.5 | 82 | 3 | 1 | 17 | 12 | 7 | 5 |
| | Feb. 15–16 | 500 | 37.5 | 118 | 4 | 2 | 5 | 10 | 7 | 8 |
| | Mar. 2– 3 | 500 | 37.5 | 152 | 0 | 0 | 00 | 15 | 8 | 5 |
| | Mar. 23–24 | 500 | 37.5 | 121 | 3 | 1 | 31 | 13 | 6 | 32 |

[a] The gasometer and mask, with the subject in the lying position, were used in all but the 1917 experiments with A. In these 5 experiments, the observations were carried on throughout the night with the clinical respiration chamber and the subject in the lying position.

[b] Given in 7 portions, i. e., 510 c. c. in the first injection, followed at intervals by 6 portions of 50 c. c. each.

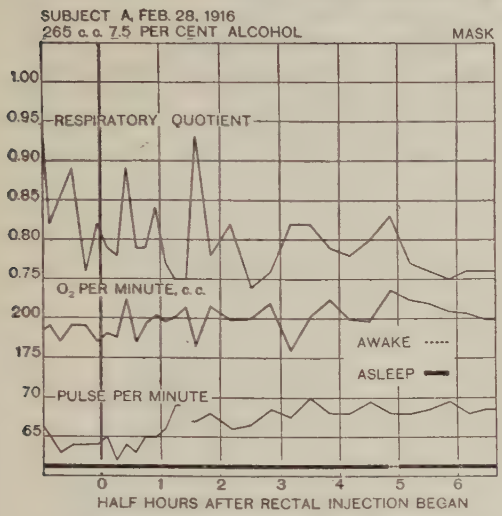
All of these experiments were carried out by the usual gasometer and mask method, with the subject lying on a couch, and continuous observations. The sleep-recording device was also used. In addition to these observations, 5 experiments were made with the clinical respiration chamber, in which 500 c. c. of a 7.5 per cent alcohol solution were injected. Of the 13 experiments, A served as subject in 8, C in 4, and D in 1. The statistics regarding the observations with a 7.5 per cent alcohol solution are given in table 24, grouped according to the amount given and the apparatus employed. The experiments with the gasometer method are first discussed.

## OBSERVATIONS WITH GASOMETER AND MASK METHOD.

### Results of Measurements Before Rectal Injection.

These experiments were carried out under practically the same conditions as those for the two previous groups, that is, the subject came in the latter

part of the afternoon, having had a meal either in the morning or at noon. The latest time at which food was taken was 2 p. m. (C, March 1 and March 22) and the nearest to the experimental period was 7h 30m a. m. (C, April 18) with the first period of the experiment beginning at 10h 03m a. m. The graphic records of the results are given in figures 41 to 48.

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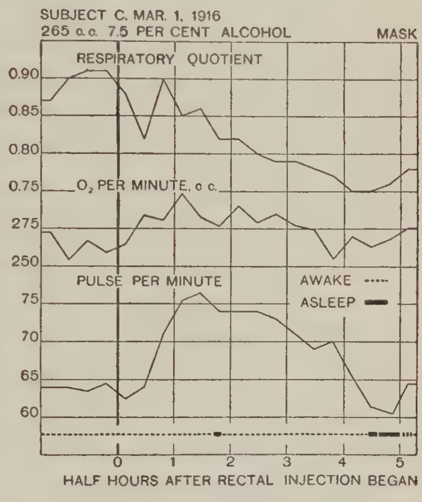


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FIG. 41.—Respiratory quotient, oxygen absorption, and pulse-rate of subject A, February 28, 1916, before and after rectal injection of 265 c. c. of a 7.5 per cent alcohol solution. (Mask, with continuous observation.)

The horizontal line at the bottom of this and subsequent charts gives a record of sleep, the solid portions indicating when the subject was asleep and the broken portions when he was awake.

FIG. 42.—Respiratory quotient, oxygen absorption, and pulse-rate of subject C, March 1, 1916, before and after rectal injection of 265 c. c. of a 7.5 per cent alcohol solution. (Mask, with continuous observation.)

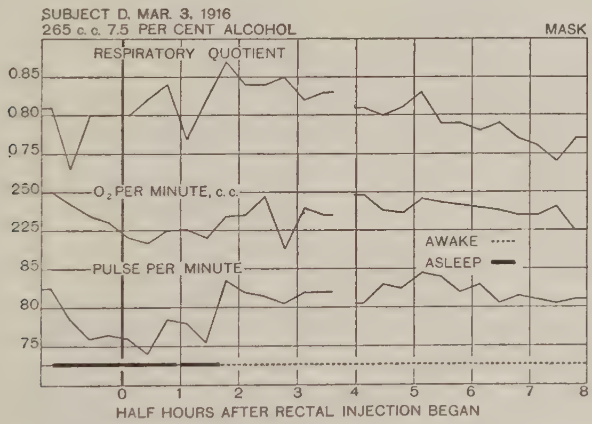



FIG. 43.—Respiratory quotient, oxygen absorption, and pulse-rate of subject D, March 3, 1916, before and after rectal injection of 265 c. c. of a 7.5 per cent alcohol solution. (Mask, with continuous observation.)

*Pulse-rate.*—The average pulse-rate for subject A in the preliminary periods of the three experiments varied from 64 to 68 beats, this being very close to his basal pulse-rate of 64 beats. With C the average varied from 59 on March 22 to 76 beats on April 18. No cause is known for the high pulse-rate with C on April 18. In the one experiment with D, the average pulse-rate for the preliminary periods was 78 beats which is about this subject's rate in the waking condition.

*Oxygen absorption.*—The oxygen absorption for subject A varied on the average in the preliminary periods from 181 c. c. per minute on April 10 to 215 c. c. per minute on April 15; with subject C, the average preliminary values ranged from 264 to 281 c. c.; with subject D, the average preliminary oxygen absorption was 239 c. c.

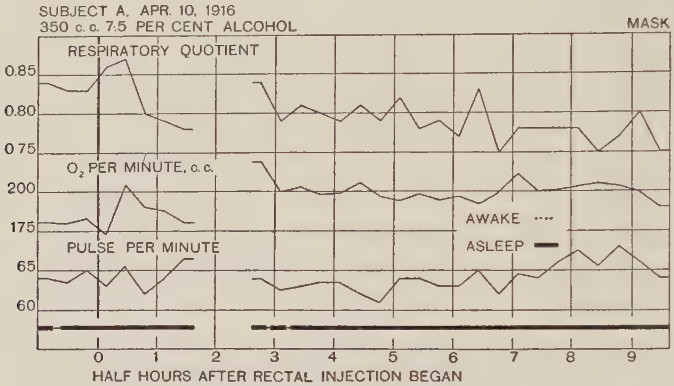



FIG. 44.—Respiratory quotient, oxygen absorption, and pulse-rate of subject A, April 10, 1916, before and after rectal injection of 350 c. c. of a 7.5 per cent alcohol solution. (Mask, with continuous observation.)

*Respiratory quotient.*—The average respiratory quotient with subject A was 0.83 in the preliminary periods for all the experiments. Subject C varied from 0.80 on April 18 to 0.90 on March 1. No particular reason is known for the high average respiratory quotient with this subject before injection on March 1. The average preliminary quotient for subject D on March 3 was 0.78. Thus, with the exception of C on March 1, the average respiratory quotients before injection were all within the range that might be expected for basal conditions, although the experiments were not strictly basal in that they were carried out usually in the evening and within 5 or 6 hours of the last meal.

### RESULTS OF MEASUREMENTS AFTER RECTAL INJECTION OF A 7.5 PER CENT ALCOHOL SOLUTION.

*Pulse-rate.*—The pulse-rate in practically all of the experiments shows a rise after injection which was apparently due to the influence of alcohol injected rectally. In three experiments the subject was asleep most of the time, so that the pulse-rate is comparable from beginning to end. In all of these three experiments (with subject A, February 28, April 10, and 15) the pulse-rate rose. With the smallest quantity of 265 c. c., representing about 20 grams of alcohol, there was a positive rise of about 5 beats per minute and

increases of about the same order of magnitude were found in the other two experiments.

Of the experiments in which the subject was asleep only part of the time, that with C on March 22 gave the most positive results, with a change from 58 beats when the subject was asleep to about 63 beats when he awoke. This rise continued until it reached the height of 75 beats in the course of $2\frac{1}{2}$ to 3 hours, thus indicating a very definite increase of heart-rate due to the injection of 400 c. c. of the solution, or about 30 grams of alcohol.

Three of the other experiments (with subject C on March 1 and 29, and with subject D on March 3) likewise exhibit increases in the pulse-rate which can hardly be ascribed solely to subjective impressions or to changes in the conditions as to sleep. The only experiment in which no change due to the alcohol is apparent is that with C on April 18, which is complicated by two long periods of sleep. When the amount of alcohol given is considered, the absence of alcohol effect is surprising.

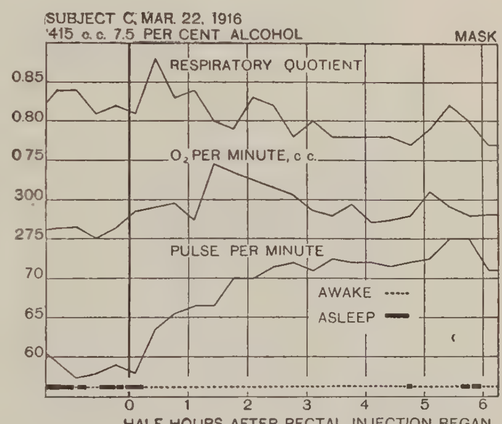



**FIG. 45.—Respiratory quotient, oxygen absorption, and pulse-rate of subject C, March 22, 1916, before and after rectal injection of 415 c. c. of a 7.5 per cent alcohol solution. (Mask, with continuous observation.)**

*Oxygen absorption.*—While in some of the experiments the injection of the 7.5 per cent solution of alcohol produced a slight increase in the oxygen absorption, this factor was apparently less influenced than any of the three measured. In the first experiment with 265 c. c. (about 20 grams of alcohol), in which subject A was asleep the entire period, there was a slight rise in the oxygen absorption. The same was true with subject D on March 3 and with subject A on April 10. In the experiment with subject D on March 3 there was a complication at the beginning of the experiment due to sleep, but if the period of wakefulness after the sleep is compared with the period after interruption due to urinating, it will be seen that in the latter case there was a slightly higher average oxygen absorption than in the period before the interruption. With subject A, on April 10, the average oxygen absorption subsequent to the interruption due to urinating was very materially higher than that preceding it. It is doubtful if any experiments other than those cited show an increase in the oxygen absorption due to the injection of a 7.5 per cent alcohol solution.

*Respiratory quotient.*—The respiratory quotient in practically all of the experiments with a 7.5 per cent alcohol solution, with the exception of that with C on April 18, was found to be from 0.03 to 0.07 or 0.08 lower after the

injection. As pointed out in the introduction of this section, the theoretical effect of alcohol upon the respiratory quotient when alcohol is utilized is a depression of the respiratory quotient depending in extent upon the amount of alcohol actually burned. The lowering which occurs here is thus in agreement with the theoretical possibilities, and it is evident from the depression of the respiratory quotient that alcohol is utilized by the subject. This lowering was evident even with the smaller quantities, namely, 265 c. c., and was very marked in some of the experiments. The fall began anywhere from 1½ to 2 hours after the injection and was apparent even when sleep occurred in the preliminary period or in the first part of the experiment and was then followed by a period of wakefulness. The sleep tended to depress the quotient but, in spite of this, the quotient was lower in periods in which the subject was awake than in periods in which he was asleep, indicating that the respiratory quotient was decidedly depressed by the injection of the 7.5 per cent alcohol solution. This effect was found even when the quantities given

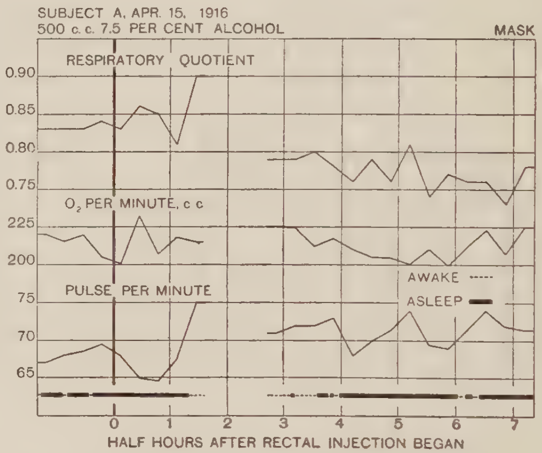



**Fig. 46.**—Respiratory quotient, oxygen absorption, and pulse-rate of subject A, April 15, 1916, before and after rectal injection of 500 c. c. of a 7.5 per cent alcohol solution. (Mask, with continuous observation.)

were smaller than those used with the 5 per cent alcohol solution. The conclusion may therefore be drawn that a 7.5 per cent alcohol solution is more effective in lowering the respiratory quotient when the substance is injected rectally than the same weight of alcohol in a 5 per cent solution.

### Discussion of Composite Chart and General Conclusions.

A composite chart giving average curves for experiments with a 7.5 per cent solution of alcohol has been prepared in the same manner as those for the preceding series of experiments. This is given in figure 49. It includes only those experiments with a 7.5 per cent alcohol solution in which the mask and gasometer method was used. It must be noted that the amounts of alcohol given in these experiments (from 19.9 to 60.8 grams) were, on the whole, slightly or considerably higher than those in the experiments with the 5 per cent solution. We thus have to consider both the effect of concentration and the effect of the total amount of alcohol.

*Pulse-rate.*—The pulse-rate for this group of experiments was slightly higher during the preliminary period than the pulse-rate preceding the sodium-chloride experiments. It was, however, about the same as for the

5 per cent alcohol solution. During the preliminary period there was a steady fall which continued nearly through the first half hour after injection. The pulse then rose until it reached the level of the pulse-rate at the beginning

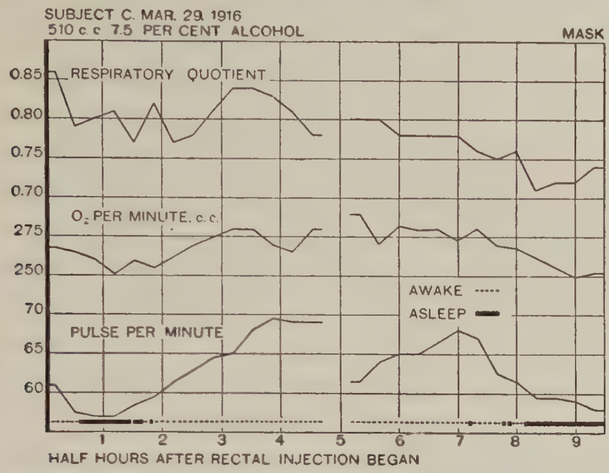



FIG. 47.—Respiratory quotient, oxygen absorption, and pulse-rate of subject C, March 29, 1916, after rectal injection of 510 c. c. of a 7.5 per cent alcohol solution. (Mask, with continuous observation.)

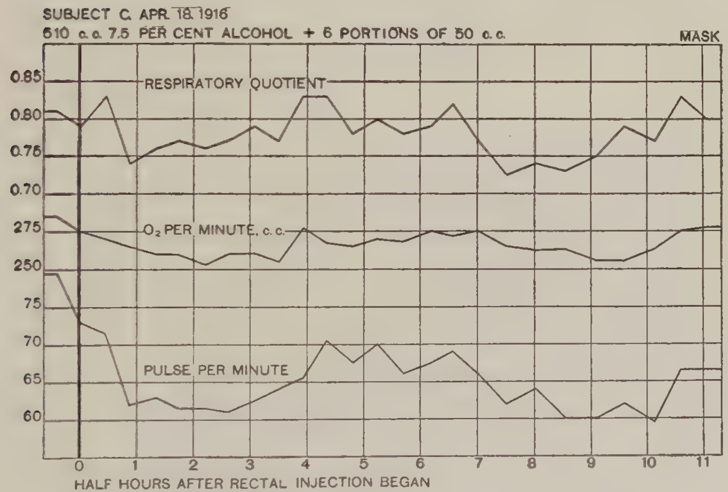



FIG. 48.—Respiratory quotient, oxygen absorption, and pulse-rate of subject C, April 18, 1916, before and after rectal injection of 510 c. c. of a 7.5 per cent alcohol solution, followed at intervals by six portions of 50 c. c. each. (Mask, with continuous observation.)

The first injection was begun at $10^h\,22^m$ a. m.; the subsequent injections of 50 c. c. each began at $11^h\,41^m$ a. m., $12^h\,22^m$, $1^h\,07^m$, $1^h\,42^m$, $2^h\,22^m$, and $2^h\,55^m$ p. m., respectively.

of the preliminary period. The average pulse during the last 3 hours was 4 beats higher than the pulse-rate at the time of injection or in the half hour subsequent to it. In contrast to the course of the pulse-rate during the

sodium-chloride experiments, there was thus a rise instead of a fall, indicating a definite increase in pulse-rate due to the injection of a 7.5 per cent alcohol solution.

*Oxygen absorption.*—The average oxygen absorption was about the same in the preliminary period as in the two preceding composite charts. It began rising immediately after the injection from 237 c. c. to a maximum of 255 c. c. This increase was somewhat greater than that obtained with the 5 per cent alcohol solution. At the end of 2½ hours it began to fall, but 4 hours after injection it had not reached the level found at the time of injection. There was accordingly an increase in the oxygen absorption as a result of giving the 7.5 per cent alcohol solution, which took place within an hour of the injection. As the calorific value of oxygen when used in burning alcohol is 4.85 per liter, the same as that for a combination of fat and carbohydrate with a respiratory quotient of 0.84, this means not only an increase in oxygen absorption, but also an increase in heat produced.

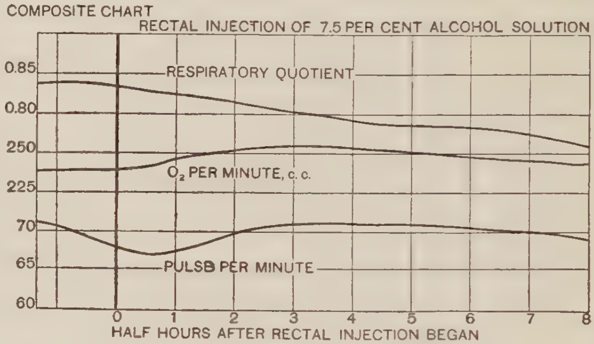



FIG. 49.—Chart showing composite results for measurements of respiratory quotient, oxygen absorption, and pulse-rate in 8 experiments with rectal injection of 20 to 60 grams of alcohol in a 7.5 per cent solution. (Mask.)

*Respiratory quotient.*—The respiratory quotient during the preliminary period was fairly high, i. e., about 0.84. It gradually fell after the injection of the alcohol, the fall continuing throughout the whole 4 hours. The quotient at the end was 0.76, or a decrease of 0.08 during the course of 4 hours. This indicates very clearly the utilization of alcohol, for, if it is used, the respiratory quotient will fall, as the theoretical respiratory quotient of alcohol is 0.667, which is lower than the respiratory quotient for fat or for carbohydrate.

The general effect of the introduction of a 7.5 per cent alcohol solution by rectum in quantities up to 800 c. c. is to increase the pulse-rate and the oxygen absorption, and to lower the respiratory quotient in a greater degree than does 500 c. c. or less of a 5 per cent alcohol solution. As pointed out before, we have to do here with an increase in both concentration and total quantity of alcohol. The experiments are not sufficient in number or in character, however, to distinguish between the effect of greater quantities of alcohol and the effect of greater concentration.

## OBSERVATIONS WITH CLINICAL RESPIRATION CHAMBER.[1]

In the five experiments in which the clinical respiration chamber was employed, only subject A was used and 500 c. c. of the 7.5 per cent alcohol

[1] An abstract of the results of the measurements of the oxygen absorption and pulse-rate has been given by Miles: Carnegie Inst. Wash. Pub. No. 333, 1924, p. 121.

solution were injected in every instance. (See table 24.) The subject remained in the apparatus during the night and the duration of the injection was longer than in all but one of the gasometer and mask experiments in which the 7.5 per cent alcohol solution was used. The curve for the carbon-dioxide production is added to those for the other factors in the graphic records in figures 50 to 54. All but one of the experiments were preceded or followed or both by short observations with the gasometer and mask. The

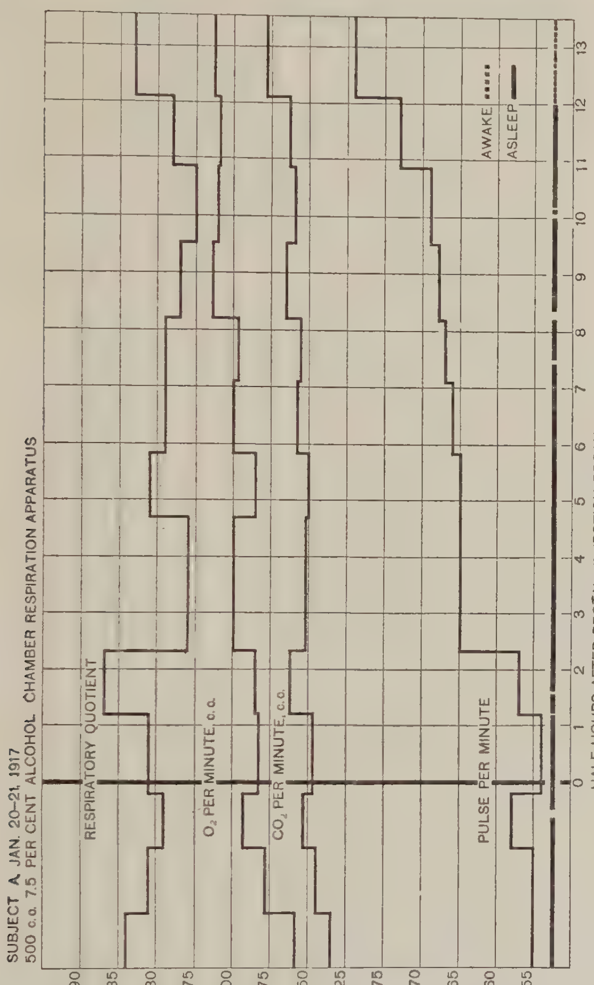



Fig. 50.—Respiratory quotient, oxygen absorption, carbon-dioxide elimination, and pulse-rate of subject A, January 20–21, 1917, before and after rectal injection of 500 c. c. of a 7.5 per cent alcohol solution. (Chamber respiration apparatus.)

The horizontal line at the bottom of this and subsequent charts gives a record of sleep, the solid portions indicating when the subject was asleep and the broken portions when he was awake.

results of these morning and evening experiments are given in short curves preceding or following the longer curves for the night experiments. The observations on February 15–16, March 2–3, and March 23–24 were preceded and followed by psychological tests connected with another research. The heart-rate was also determined at intervals throughout the night by means of standard electro-cardiograms,[1] as was done in certain of the sodium-

[1] For a detailed account of these psychological tests and the standard electro-cardiograms, see Miles: loc. cit., pp. 111–124.

chloride experiments. (See p. 97.) Accordingly, in addition to the pneumographs and stethoscope, the subject wore cheese-cloth bandages, moistened in a solution of sodium chloride, around the left ankle and the two wrists, which were connected with the rest of the electro-cardiographic outfit.

*Pulse-rate.*—The pulse-rate in the control experiments with the clinical chamber rose or fell but little during the night. The mask was applied to

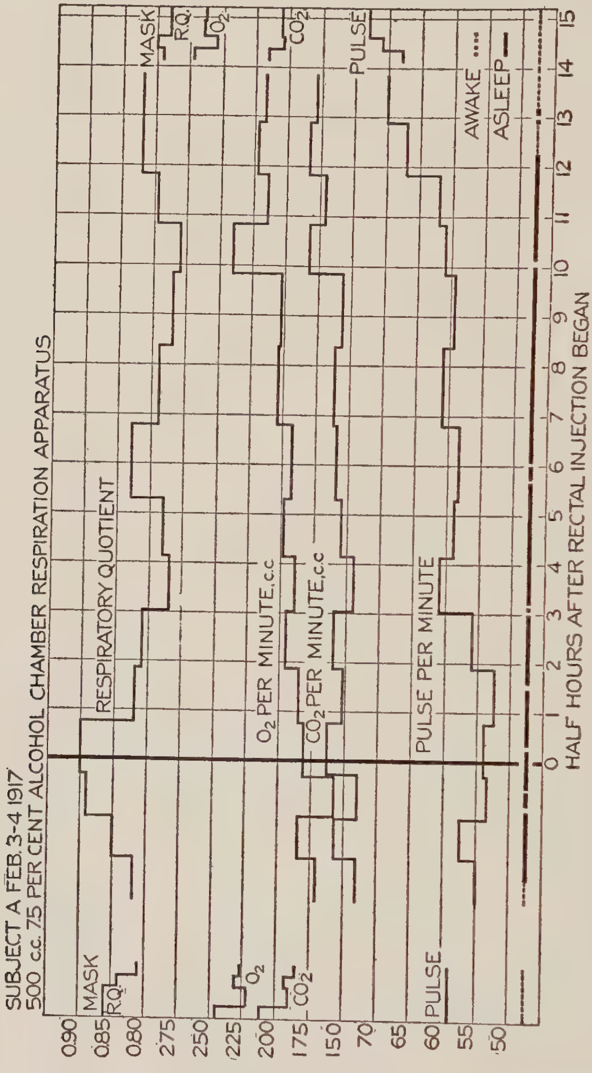



Fig. 51.—Respiratory quotient, oxygen absorption, carbon-dioxide elimination, and pulse-rate of subject A, February 3–4, 1917, before and after rectal injection of 500 c. c. of a 7.5 per cent alcohol solution. (Chamber respiration apparatus, preceded and followed by observations with mask and gasometer apparatus.)

the subjects in all of the experiments with the chamber as soon as possible with minimum amount of effort on the part of the subject, and measurements commenced immediately. (See figs. 20 to 23.) In contrast with these observations, the most striking results for the chamber experiments in which 500 c. c. of a 7.5 per cent alcohol solution (37.5 grams) were injected rectally were found with the pulse-rate. In the five experiments this invari-

ably rose after the injection, with a maximum increase of over 20 beats. Although the experiments continued over a period of about 7 hours after the injection began, in only one (March 2–3) was there any indication of a return to the pre-injection level. It must also be noted that this increase in pulse-rate occurred notwithstanding the fact that the subject was sound asleep practically the entire time.

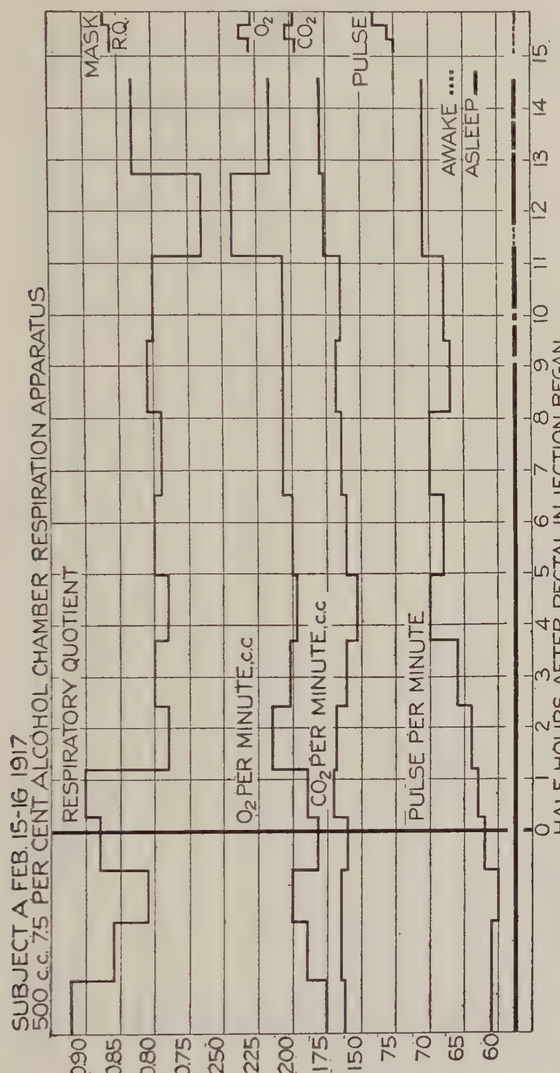



FIG. 52.—Respiratory quotient, oxygen absorption, carbon-dioxide elimination, and pulse-rate of subject A, February 15–16, 1917, before and after rectal injection of 500 c. c. of a 7.5 per cent alcohol solution. (Chamber respiration apparatus, followed by observations with mask and gasometer apparatus.)

On January 20–21, the average pulse-rate before any effect due to alcohol became apparent was about 56 beats; it rose abruptly to 65 beats during the second hour after injection, and then gradually increased until at the end of the sixth hour after injection it was 73 beats. After the subject woke the rate rose still higher to 79 beats.

On February 3–4, the general average before any effect due to the injection

of the alcohol was about 54 beats. At the end of 2 hours it rose to about 60 beats and remained at this level until the subject awoke at the end of the sixth hour, when it rose to 68 beats and later to 70 beats. There was thus a change from 54 to 70 beats in the course of the experiment. The short periods with the mask in the morning had about the same pulse-rate as the last period with the clinical chamber.

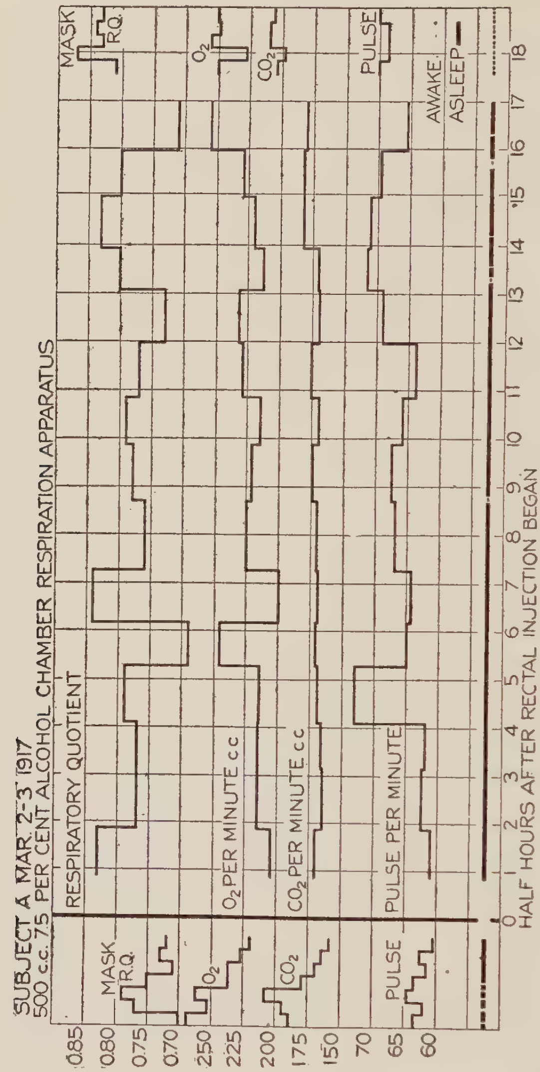



Fig. 53.—Respiratory quotient, oxygen absorption, carbon-dioxide elimination, and pulse-rate of subject A, March 2–3, 1917, before and after rectal injection of 500 c. c. of a 7.5 per cent alcohol solution. (Chamber respiration apparatus, preceded and followed by observations with mask and gasometer apparatus.)

On February 15–16, the average pulse-rate before injection was 62 beats per minute. In the course of 2 hours after injection the rate rose to 70 beats and remained at practically this level throughout the night. In the observations with the gasometer and mask combination in the morning, with the subject awake, the average pulse-rate was 76 beats.

On March 2–3, there were no periods with the clinical respiration chamber

preliminary to the injection, although 7 periods with the mask and gasometer preceded it. The pulse-rate in the gasometer and mask experiments was about 63 beats per minute, and was practically the same in the chamber experiment in the first 2 hours after injection. It rose thereafter for a short time to 73 beats, then dropped to a level of 65 beats, until during the seventh and eighth hours after injection when it averaged about 70 beats. In the

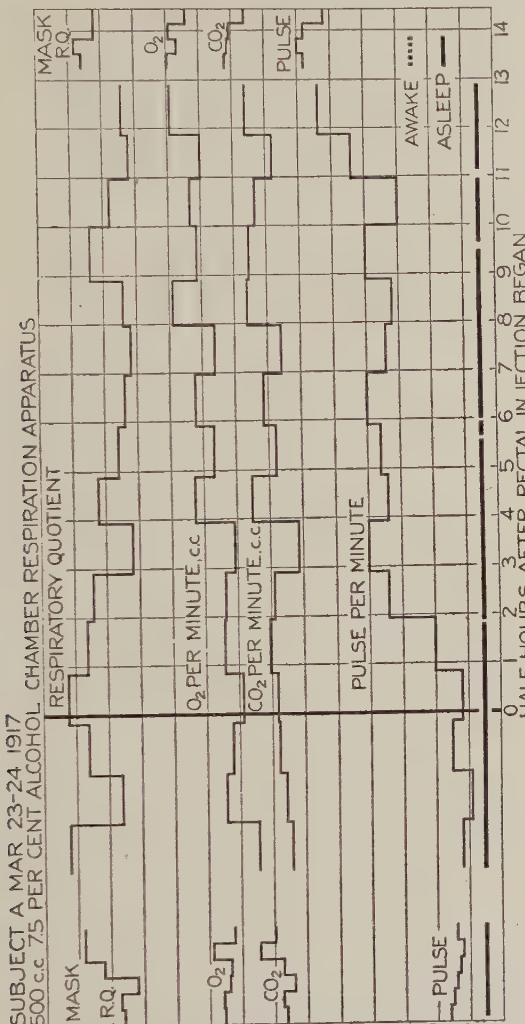



Fig. 54.—Respiratory quotient, oxygen absorption, carbon-dioxide elimination, and pulse-rate of subject A, March 23–24, 1917, before and after rectal injection of 500 c. c. of a 7.5 per cent alcohol solution. (Chamber respiration apparatus, preceded and followed by observations with mask and gasometer apparatus.)

supplementary experiments in the morning with the mask and gasometer and the subject awake, the pulse-rate averaged 69 beats.

On March 23–24, in the periods with the mask and gasometer when the subject was asleep and before injection took place, the average pulse-rate was 67 beats and continued at about this level during the periods in the chamber before injection. Within 2 hours after the injection the pulse-rate

rose from a level of 66 beats to 80 beats, and remained between 80 and 75 beats much of the entire night until the last two periods in the morning, when it rose to 82 and 87 beats. In the morning periods with the mask and gasometer, and with the subject awake, the pulse-rate was on the same level as during the last period in the chamber.

This marked effect upon the pulse-rate after alcohol injection is therefore a positive one and confirms the changes in pulse-rate which were obtained in the experiments with the mask and gasometer combination.

*Oxygen absorption and carbon-dioxide elimination.*—The oxygen absorption after the injection of 500 c. c. of a 7.5 per cent alcohol solution by rectum was increased in the course of 5 or 6 hours in some cases as much as 20 per cent. This change was very gradual but was positive in practically all of the experiments. The increase is somewhat confirmed by a more gradual rise in the carbon-dioxide elimination.

*Respiratory quotient.*—The respiratory quotient in the five chamber experiments was lowered as a result of the injection of a 7.5 per cent solution of alcohol, this fall amounting at times to as much as 0.05 and 0.07 in the course of 3 or 4 hours. The lowest level appeared to be reached about 5 to 6 hours after the injection began, with an indication of a rise at the end of the fifth and sixth hours. In these experiments the effect is absolutely clear in contrast to the results obtained with the 7.5 per cent solution in experiments with the gasometer apparatus and short periods. As the subject was asleep practically the whole period of observation in the chamber experiments, the results of the alcohol injection were not obscured by changes from sleep to waking. In the experiments with the clinical chamber (see p. 102), in 2 of which sodium chloride was injected, there was a very slight (0.03) increase in the respiratory quotient during the night. With the 7.5 per cent alcohol solution there was a depression of the respiratory quotient. This depression corresponds to the theoretical effect of the utilization of alcohol in metabolism, namely, a lowering of the respiratory quotient. The effects of the injection of alcohol in these experiments in depressing the respiratory quotient are therefore clearly defined.

### Discussion of Composite Chart of Chamber Experiments.

A composite chart has been drawn of the results of the five experiments in which 500 c. c. of a 7.5 per cent alcohol solution were injected rectally while subject A was in the chamber respiration apparatus. (See fig. 55.) The averages are drawn for an hour before injection and for 6½ hours after the injection began and give results for the respiratory quotient, oxygen absorption, and pulse-rate per minute.

*Pulse-rate.*—The pulse-rate during the first hour before injection was between 61 and 62 beats. It rose gradually after injection and for 2 hours there was a steady rise, the average value at the end of 2 hours being about 68 beats. Subsequently it rose steadily, but at a much slower rate for the next 3 hours, reaching at the end of that time 70 beats per minute. When the observations were concluded 6½ hours after the beginning of the injection, the pulse-rate was still rising, with an average of about 73 beats per minute. There was, therefore, on the average, a steady rise in the pulse-rate after the injection of 500 c. c. of a 7.5 per cent alcohol solution.

*Oxygen absorption.*—The oxygen absorption during the preliminary hour

averaged about 185 c. c. Then 1 hour after injection began it rose to 200 c. c. per minute. From then on throughout the rest of the 6½ hours after injection there was a slow and gradual rise. At the end of 6½ hours there was a value of about 225 c. c. so that there was a rise of 40 c. c. per minute in the oxygen absorption due to the ingestion of 500 c. c. of a 7.5 per cent alcohol solution.

*Respiratory quotient.*—The average respiratory quotient for the hour before injection began was somewhat high for this particular subject, being 0.84. The respiratory quotient after the first half hour fell markedly, and at the end of the second hour had reached 0.78, at which point it remained for the rest of the experimental period. There was therefore a total fall of 0.06 due to the injection of 500 c. c. of a 7.5 per cent alcohol solution.

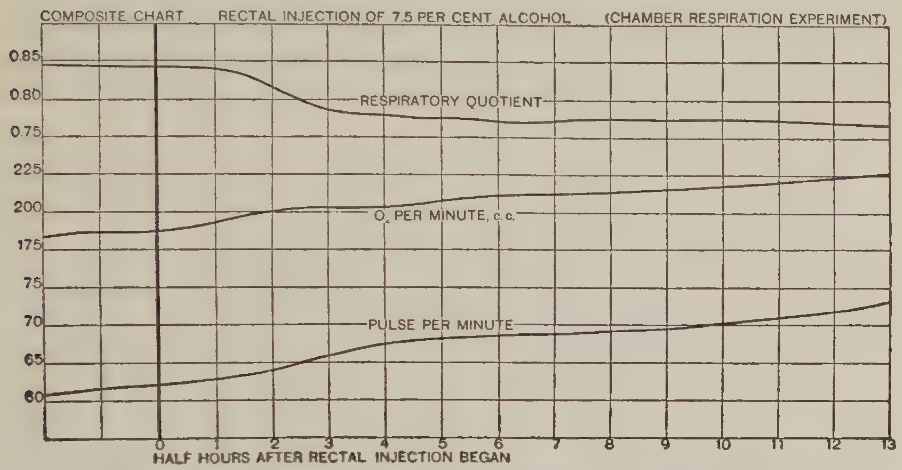



Fig. 55.—Chart showing composite results for measurements of respiratory quotient, oxygen absorption, and pulse-rate in 5 experiments with rectal injection of 37.5 grams of alcohol in a 7.5 per cent solution. (Clinical respiration chamber.)

As a whole, therefore, the composite chart shows definite changes due to the injection of 37.5 grams of alcohol in the form of a 7.5 per cent alcohol solution. These changes are a marked increase in the pulse-rate, a lower respiratory quotient, and a marked increase in oxygen absorption.

GENERAL SUMMARY OF RESULTS WITH A 7.5 PER CENT ALCOHOL SOLUTION.

Both groups of experiments, namely, those with the mask and gasometer and those with the clinical respiration chamber, indicate that a 7.5 per cent alcohol solution in quantities varying from 250 c. c. to 500 c. c. increases markedly the pulse-rate and lowers the respiratory quotient. This effect continues for a period as long as 6 or 7 hours in some experiments and begins as early as 1 hour after the beginning of the injection. When the quantity is as large as 500 c. c., the oxygen absorption is increased nearly 20 per cent, indicating both a utilization of alcohol by the subject and a stimulating influence of alcohol upon the total metabolism.

### Experiments with a 10 per cent Alcohol Solution.

Four experiments with 260 to 265 c. c. of a 10 per cent alcohol solution introduced rectally were made with three subjects, A, C, and D. The general details of the observations are given in table 25. The duration of injection was recorded in but three experiments, with variation between 1 minute and 26 minutes. The number of periods before injection ranged between 3 and 6, and the time covered from 30 minutes to 1 hour. The periods after the beginning of the injection varied in number from 14 to 21, and in the duration of observation after alcohol from 2 hours and 20 minutes to 3 hours and 40 minutes. The gasometer and mask apparatus and the sleep recorder were used in all of the experiments. The statistics of the experiments are given in table 25 and the results graphically recorded in figures 56 to 59. The conditions of these experiments were the same as in the previous group. All four experiments were made in the latter part of the afternoon and early evening. The last meal was in all cases between $1^h\,15^m$ and 2 p. m., and in three of the four experiments the beginning of the first period was less than a half-hour after the subject lay down.

Table 25.—*Statistics of respiratory exchange observations before and after the injection by rectum of a 10 per cent alcohol solution.*

| Subject. | Date.[a] | Alcohol injected. | | Duration of injection. | Periods before injection. | | Periods after injection. | |
|---|---|---|---|---|---|---|---|---|
| | | Volume of solution. | Weight of alcohol. | | No. | Time covered. | No. | Time covered. |
| | 1916. | *c. c.* | *gm.* | *min.* | | *h. min.* | | *h. min.* |
| A | Mar. 6 | 265 | 26.5 | 23 | 5 | 0 50 | 21 | 3 30 |
| | Mar. 24 | 260 | 26.0 | .. | 6 | 1 00 | 14 | 2 20 |
| C | Mar. 8 | 265 | 26.5 | 1 | 3 | 0 30 | 16 | 3 00 |
| D | Mar. 10 | 265 | 26.5 | 26 | 5 | 0 50 | 20 | 3 40 |

[a] The gasometer and mask method, with the subject in the lying position, was used in all of these experiments.

## RESULTS OF MEASUREMENTS BEFORE RECTAL INJECTION.

### Pulse-Rate.

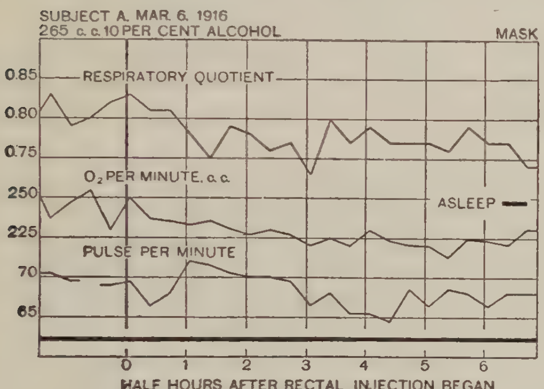
The average pulse-rate in the periods before injection with subject A was 70 beats on March 6 and 64 beats on March 24. The pulse-rate on March 6 was rather high for an average and the value for the preliminary oxygen absorption was also high. The last meal on this day was at 2 o'clock, about $3\frac{1}{2}$ hours before the experiment began, and was fairly abundant. The fact that the respiratory quotient was not high and did not fall gradually indicates that the high metabolism was not due to the influence of a previous mixed meal. If the preceding meal had contained a large amount of protein, it would account for the increased oxygen consumption, but the subject's report gave no evidence of this. Consequently, it is difficult to explain why the metabolism of the subject was so high at this period of the day. The preliminary pulse-rate for D was 78 beats per minute and the average for C was 65 beats, which is close to his basal pulse-rate.

### Oxygen Absorption.

As pointed out in the paragraph above, the average oxygen absorption with A before injection on March 6 was high, 242 c. c. This high metabolism is not easy to explain. As already noted, the pulse-rate at the beginning of the experiment was higher than usual. The oxygen absorption in the experiment of March 24 was 209 c. c. which is near the average basal oxygen absorption for this subject. The average absorption for C on March 8 was 266 c. c. in the periods before injection; for D (March 10) it was 226 c. c. These figures are near the average preliminary values which have previously been discussed.

### Respiratory Quotient.

The preliminary respiratory quotients in the two experiments with subject A were 0.81 and 0.77, respectively; for C on March 8, 0.82, and for D, 0.83. The respiratory quotients before injection were therefore all normal for the conditions under which these experiments were carried out.

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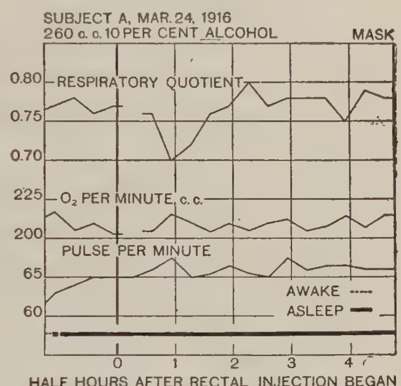


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Fig. 56.—Respiratory quotient, oxygen absorption, and pulse-rate of subject A, March 6, 1916, before and after rectal injection of 265 c. c. of a 10 per cent alcohol solution. (Mask, with continuous observation.)

The horizontal line at the bottom of this and subsequent charts gives a record of sleep, the solid portions indicating when the subject was asleep and the broken portions when he was awake.

Fig. 57.—Respiratory quotient, oxygen absorption, and pulse-rate of subject A, March 24, 1916, before and after the rectal injection of 260 c. c. of a 10 per cent alcohol solution. (Mask, with continuous observation.)

## RESULTS OF MEASUREMENTS AFTER RECTAL INJECTION OF A 10 PER CENT ALCOHOL SOLUTION.

Two of the experiments with a 10 per cent alcohol solution were made with subject A. In his first experiment the subject was asleep during the entire period, with slight restlessness at the first. Within the first hour after the beginning of the alcohol injection there was a marked fall in the respiratory quotient from a general level of 0.81 to 0.75, the lower level continuing for the rest of the experiment. In the second experiment with the same subject (March 24), there was an interruption in the values immediately after the giving of alcohol, with a sharp decline in the respiratory quotient in the first

half hour. However, the quotient rose again, so that if the first hour after the injection were omitted, there would be practically no significant variation in the respiratory quotient during the whole experiment. The oxygen absorption was apparently not affected in the experiment on March 6, since it did not increase, though there was a very gradual but slight descent. In the experiment on March 24, also, it was not affected. The pulse-rate in the experiment on March 6 was hardly, if any, influenced by the alcohol, while in the experiment of March 24 it was raised slightly.

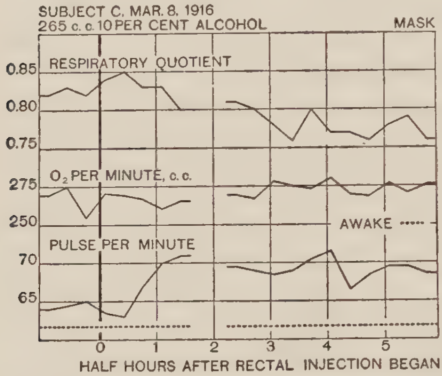



FIG. 58.—Respiratory quotient, oxygen absorption, and pulse-rate of subject C, March 8, 1916, before and after rectal injection of 265 c. c. of a 10 per cent alcohol solution. (Mask, with continuous observation.)

The experiment with C (March 8) was fortunately uncomplicated by sleep, as the subject was awake the entire time. Within the first hour after the alcohol was given there was a decided fall in the respiratory quotient from an average of 0.82 until it reached 0.77 in the second hour. The pulse-rate rose materially, i. e., about 5 beats, but part of this increase was due to a desire to urinate, though the high level continued, with some variation, even after urination. The oxygen absorption was little affected by the alcohol injection, its subsequent course being even.

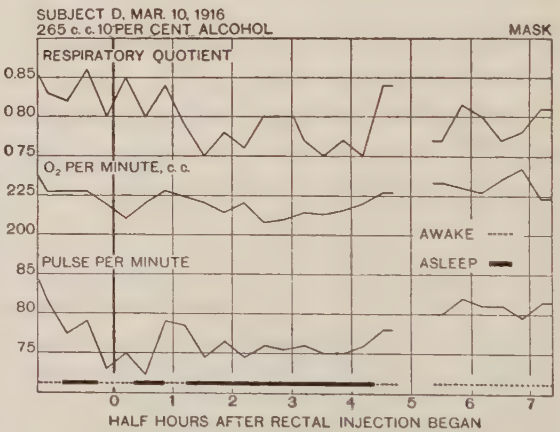



FIG. 59.—Respiratory quotient, oxygen absorption, and pulse-rate of subject D, March 10, 1916, before and after the rectal injection of 265 c. c. of a 10 per cent alcohol solution. (Mask, with continuous observation.)

In the experiment with subject D, the respiratory quotient fell to 0.75 within the first hour after the injection of the alcohol and continued near this point up to the last period before the interruption, when it rose again to about the preliminary level. After the intermission it returned to ap-

proximately the average lower level, even though the subject was awake. This experiment is partly complicated by sleep, but the influence of the alcohol does not seem to be obscured by this factor. The oxygen absorption was not affected to any great extent. The pulse-rate was definitely lower immediately after the injection and was then slightly raised; during the last hour of the experiment it was materially higher than in the period immediately following the giving of the alcohol.

The injection of 265 c. c. of a 10 per cent alcohol solution produced in three of four experiments a notable fall in the respiratory quotient. In two experiments there was a positive increase in the pulse-rate, but none of the observations gave evidence of a definite rise in the oxygen absorption. The effect of these injections of a 10 per cent solution is, however, more marked than the effect of the 5 per cent solution containing about the same amount of alcohol. (See p. 111.)

### DISCUSSION OF COMPOSITE CHART OF EXPERIMENTS WITH A 10 PER CENT ALCOHOL SOLUTION.

A composite chart of the results of the four experiments with a 10 per cent alcohol solution is given in figure 60.

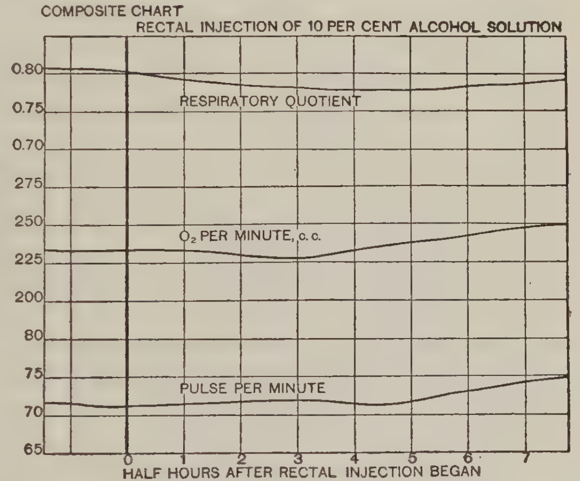



FIG. 60.—Chart showing composite results for measurements of respiratory quotient, oxygen absorption, and pulse-rate in 4 experiments with rectal injection of 26 to 26.5 grams of alcohol in a 10 per cent solution. (Mask.)

*Pulse-rate.*—The pulse-rate shows no very definite change until about 2½ hours after the injection. Thereafter until the end of the experiment (about 4 hours after the injection began) there was a slight rise.

*Oxygen absorption.*—During the preliminary period the oxygen absorption was about 235 c. c. Beginning with the third half hour after injection, there was a steady rise, so that at the end of the experiment the average value was 250 c. c.

*Respiratory quotient.*—The respiratory quotient fell very slightly from the preliminary 45 minutes until the second hour after injection, but had a tendency to rise towards the end of the experiment.

This chart is the least definite of all the composite charts in its indications of the effect of alcohol injection. The explanation for this difference may be found in the small number of experiments in the series and the relatively

large amount of sleep which in one experiment (March 6) may have exerted an unusually depressing influence on the metabolism, and in another (March 10) caused considerable variation in the results because of the alternate sleeping and waking. The tendency is toward a balanced effect upon the changes already noted as occurring in the course of the experiments and the composite does not have the distinctive features of the alcohol effect apparent in the individual experiments.

## RESPIRATORY EXCHANGE AS INFLUENCED BY ALCOHOL GIVEN BY MOUTH.

With two of the subjects, A and C, a few experiments were made in which alcohol was given by mouth, and the three concentrations employed which were used in the rectal injections, i. e., 5, 7.5, and 10 per cent. A number of observations of the respiratory exchange after alcohol taken by mouth have been made by Higgins[1] and published in an earlier communication from this Laboratory, together with a review of the previous literature on the influence of alcohol upon the respiratory exchange. Higgins gave 30 c. c. and 45 c. c. (24 and 36 grams) of alcohol in 200 c. c. of cereal coffee infusion; 25 c. c. of water were given afterwards. His measurements of the respiratory exchange were made upon 7 subjects, breathing through the mouthpiece, the short-period observations continuing from 2 to 3 hours at intervals after the alcohol and control solutions had been given. He found that in about one-fifth of the experiments there was a rise of 5 to 7 per cent in the oxygen absorption. In about 45 per cent of the experiments there was a relative acceleration of the pulse-rate. Calculations made by Higgins from the respiratory quotient indicated that 45 c. c. did not burn more rapidly than 30 c. c. and that 20 to 40 per cent of the metabolism was due to alcohol.

Miles[2] measured the oxygen consumption with the Benedict portable apparatus and also the pulse-rate approximately $2\frac{1}{2}$ to 3 hours after 27.5 grams of alcohol had been taken by mouth in 1,000 c. c. of water, alcohol-free beer, or grape-juice. Two successive measurements of 15 minutes' duration each were made, with the subject in the sitting position. In three experiments with water alone the average oxygen consumption for the two periods was 242 and 244 c. c. per minute, and the pulse-rate 65 and 68 beats per minute, respectively. With alcohol and water the oxygen consumption was 255 and 261 c. c. per minute and the pulse-rate was 72 and 73 beats per minute. When the alcohol-free beer was used, the control values for oxygen were 235 and 242 c. c., with the pulse-rate 65 and 66 beats. When 27.5 grams of alcohol were added to the beer, the oxygen values were 249 c. c. and the pulse-rates 69 beats for both periods. With grape-juice as a control, the oxygen values were 244 c. c. and 254 c. c. and the pulse-rate 64 and 66 beats, respectively. When 27.5 grams of alcohol were added, the oxygen values changed to 253 and 255 c. c., and the pulse-rates to 66 and 70 beats. Thus there was an increase in oxygen consumption and pulse-rate in all three groups of experiments, the most marked being when the alcohol was taken in water alone.

The quantity of alcohol in the Miles experiments was slightly larger than

[1] Higgins: Journ. Pharm. and Exp. Therapeutics, 1917, 9, p. 441.
[2] Miles: Carnegie Inst. Wash. Pub. No. 333, 1924, pp. 177–180.

that used for most of the experiments reported in this monograph, but the dilution was greater. Furthermore, while Higgins used cereal coffee and Miles employed water, alcohol-free beer, or grape-juice to dilute the alcohol, in the series of experiments discussed in this section the alcohol, when given by mouth, was diluted with water only and the respiratory exchange was measured continuously in short periods by use of the mask, as in many of the experiments with rectal feeding. According to the ordinary routine, preliminary observations were made for about an hour. The mask was then removed, the subject drank the solution of alcohol and water as quickly as possible, the mask was again adjusted, and the measurements were continued. In one case the mask was not removed, but the subject took the alcohol solution through a tube inserted in the mask.

TABLE 26.—*Statistics of respiratory exchange observations before and after the ingestion by mouth of 5 per cent, 7.5 per cent, and 10 per cent alcohol solutions.*

| Subject. | Date.[a] | Volume of solution and concentration. | Weight of alcohol. | Time of drinking. | Periods before alcohol. | | Periods after alcohol. | |
|---|---|---|---|---|---|---|---|---|
| | | | | | No. | Time covered. | No. | Time covered. |
| | | *c. c.* | | | | | | |
| | 1915. | *5 p. ct.* | *grams.* | *min.* | | *h. min.* | | *h. min.* |
| C | Dec. 15 | 400 | 20 | 3 | 6 | 1 00 | 24 | 3 1 |
| A | Dec. 17 | 400 | 20 | 6 | 6 | 1 00 | 21 | 2 53 |
| C | Dec. 23 | 400 | 20 | 3 | 5 | 0 49 | 20 | 2 48 |
| | 1916. | *7.5 p. ct.* | | | | | | |
| A | Mar. 27 | 250 | 18.8 | 1 | 6 | 1 00 | 25 | 3 30 |
| C | Apr. 1 | 250 | 18.8 | 1 | 0 | 0 00 | 36 | 5 30 |
| | | *10 p. ct.* | | | | | | |
| A | Apr. 20 | 250 | 25 | 4 | 5 | 0 59 | 26 | 5 55 |

[a] The gasometer and mask method, with the subject in the lying position, was used in all of these experiments.

Table 26 gives information regarding the details of these observations. Three experiments were made with 400 c. c. of a 5 per cent alcohol solution, the subjects requiring from 3 to 6 minutes to drink this quantity. The number of periods preliminary to the alcohol ingestion ranged from 5 to 6 and the time covered was from 49 minutes to 1 hour. The number of alcohol periods varied from 20 to 24 and the minimum and maximum times were 2 hours and 48 minutes and 3 hours and 1 minute.

Two experiments were made with 250 c. c. of a 7.5 per cent alcohol solution. In one of these there was no preliminary period, but the measurements were made immediately after the alcohol was taken, so that the effect might be observed over as long a period as possible. In this case the experiment continued 5 hours and 30 minutes after the alcohol was given. One experiment was also made in which 250 c. c. of a 10 per cent alcohol solution was taken by the subject, this containing 25 grams of alcohol. The preliminary period extended over 59 minutes, divided into 5 periods; the number of alcohol periods was 26 and the time covered about 6 hours. The results of the experiments on the measurements of respiratory exchange after alcohol given by mouth are presented in the form of curves (figs. 61 to 66), as in the preceding sections. The detailed discussion of the observations follows.

### Results of Measurements Before Alcohol was Taken.

The experiments with alcohol given by mouth were conducted under the same conditions as the experiments with rectal injection, that is, the subjects came to the Laboratory in the early evening or late afternoon. The latest time at which food was taken before the observations was at 1h 30m

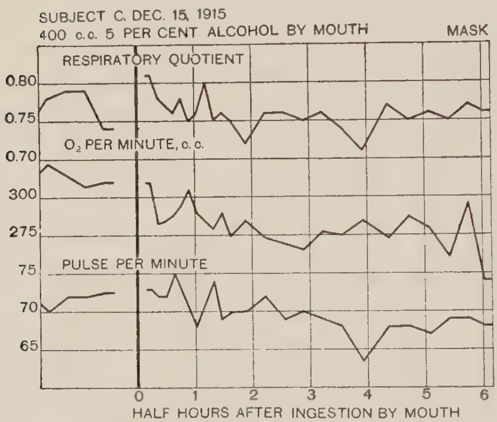



Fig. 61.—Respiratory quotient, oxygen absorption, and pulse-rate of subject C, December 15, 1915, before and after ingestion by mouth of 400 c. c. of a 5 per cent alcohol solution. (Mask, with continuous observation.)

p. m. The experiment with subject A on April 20 was made in the morning and was preceded by a very light breakfast. The results of the pre-injection periods for this experiment indicate a slightly high carbohydrate metabolism. The oxygen absorption, however, averaged only 189 c. c. for the three periods before the injection and was therefore near the average normal basal for this individual (206 c. c.).

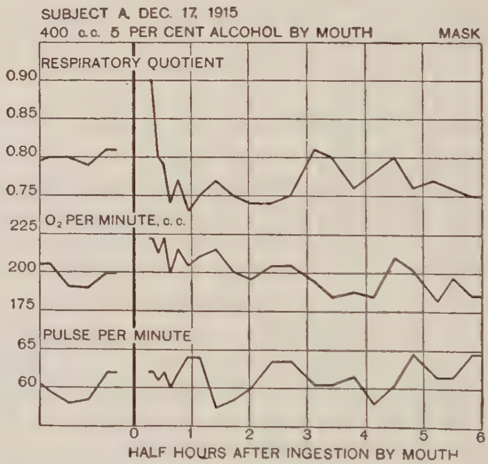



Fig. 62.—Respiratory quotient, oxygen absorption, and pulse-rate of subject A, December 17, 1915, before and after ingestion by mouth of 400 c. c. of a 5 per cent alcohol solution. (Mask, with continuous observation.)

### Pulse-Rate.

The average pulse-rate in the preliminary periods of the experiments with A varied from 60 beats on December 17 to 68 beats on March 27; the latter pulse-rate was somewhat high for this individual. The oxygen absorption, 223 c. c., was also high, with a respiratory quotient of 0.85. The last meal,

however, was at 1^h 30^m p. m. and the first period recorded on the chart began at 4^h 49^m p.m. The preliminary pulse-rates of C on December 15 and December 23 were 72 and 62 beats per minute, respectively. There were no preliminary periods on April 1.

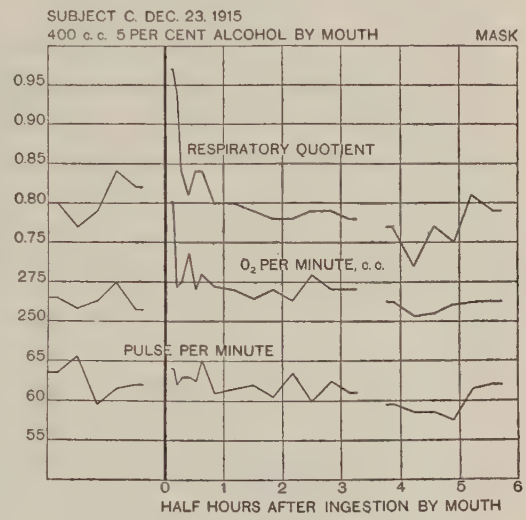



Fig. 63.—Respiratory quotient, oxygen absorption, and pulse-rate of subject C, December 23, 1915, before and after ingestion by mouth of 400 c. c. of a 5 per cent alcohol solution. (Mask, with continuous observation.)

### Oxygen Absorption.

The oxygen absorption in the preliminary periods with A varied from 189 on April 20 to 223 c. c. on March 27, the value in the third experiment being 197 c. c. per minute. The average of the oxygen-absorption values for the preliminary periods recorded on the chart for C on December 15 is 314 c.c., a very high value for the oxygen absorption of this subject, the average

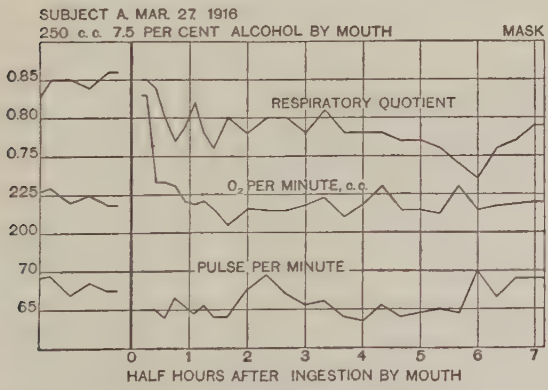



Fig. 64.—Respiratory quotient, oxygen absorption, and pulse-rate of subject A, March 27, 1916, before and after ingestion by mouth of 250 c. c. of a 7.5 per cent alcohol solution. (Mask, with continuous observation.)

preliminary value for the experiment on December 23 being only 263 c. c. The last meal on December 15 was at 7^h 45^m a. m. and the first period was at 6^h 03^m p. m.; consequently this high value can not be due to the influence of food. The respiratory quotient on that day was 0.78.

### Respiratory Quotient.

The preliminary respiratory quotients for A varied from 0.80 to 0.86; the respiratory quotients for C in two experiments were 0.78 and 0.80. The preliminary respiratory quotients in this series of mouth experiments, except in the experiments with A on March 27 and April 20, are very near the normal post-absorptive values.

### Results of Measurements After Alcohol was Taken.

In three experiments with 400 c. c. of a 5 per cent alcohol solution, one was with subject A and the other two with subject C. In the experiment with subject A on December 17 (fig. 62), the respiratory quotient fell about 0.05 within the first 20 minutes of the giving of the alcohol. After an hour and a half it rose to a level slightly higher, but did not reach the level for the preliminary period. The oxygen absorption was not materially altered by the ingestion of this amount of alcohol, falling slightly, if anything, during the subsequent second or third hour. The course of the pulse-rate was varying and showed no change of direction which could be attributed to the influence of alcohol.

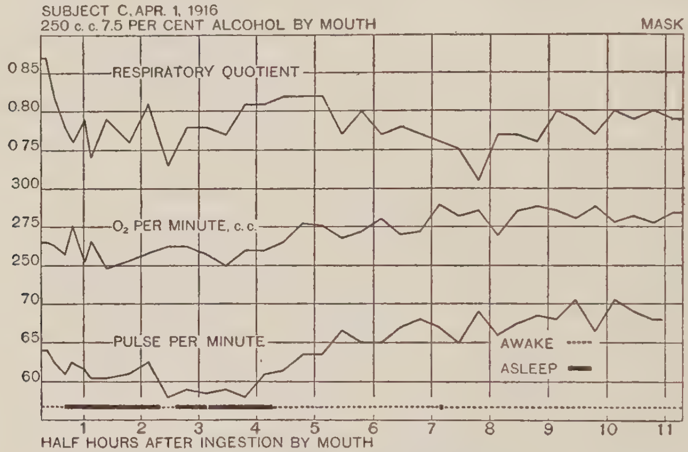



Fig. 65.—Respiratory quotient, oxygen absorption, and pulse-rate of subject C, April 1, 1916, after ingestion by mouth of 250 c. c. of a 7.5 per cent alcohol solution. (Mask, with continuous observation.)

The horizontal line at the bottom of this and subsequent charts gives a record of sleep, the solid portions indicating when the subject was asleep, and the broken portions when he was awake.

In the experiment with subject C on December 15 (fig. 61) there was a slight fall (0.02 on the average) in the second hour in the respiratory quotient. The pulse-rate fell somewhat during the experiment and there was likewise a reduction in the oxygen consumption, but apparently these changes were not due to the alcohol. In the experiment on December 23 with the same man (see fig. 63) there was very little change in the respiratory quotient in the first hour after the alcohol was taken, but in the third hour the average respiratory quotient was somewhat lower (0.03) than that during the preliminary period. The pulse-rate was not affected by the alcohol. The oxygen absorption was slightly higher in the three half hours immediately following the giving of the alcohol.

The ingestion of 400 c. c. of a 5 per cent alcohol solution by mouth thus

lowered the respiratory quotient (0.02 to 0.03) in three experiments. The oxygen consumption and heart-rate were not affected.

Two experiments were made with subjects A and C in which 250 c. c. of a 7.5 per cent alcohol solution were given. In the experiment with subject A (fig. 64) there was an immediate lowering of the respiratory quotient, and it remained at this lower level (about 0.79) until the third hour, when a still lower average respiratory quotient was found (0.77). The pulse-rate did not change until the last hour of the experiment, when it rose slightly, and the oxygen absorption was not affected. In the experiment with subject C (fig. 65) an immediate fall was found in the respiratory quotient following the alcohol, as in the experiment with A. Since there were no preliminary periods, it can not be stated definitely whether this fall was due to the taking of the alcohol or to activity preceding its ingestion. The general course of the quotient did not seem to change materially throughout the rest of the experiment, except that it tended to rise in the last hour and a half, 5 or 6 hours after the taking of the alcohol. Both the oxygen consumption and pulse-rate rose 2 or 3 hours after the alcohol was taken.

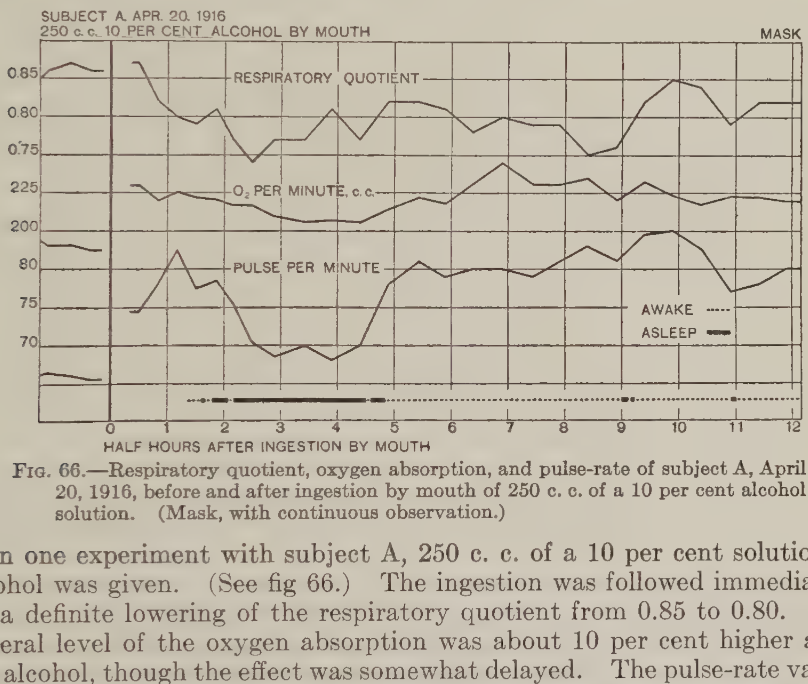



FIG. 66.—Respiratory quotient, oxygen absorption, and pulse-rate of subject A, April 20, 1916, before and after ingestion by mouth of 250 c. c. of a 10 per cent alcohol solution. (Mask, with continuous observation.)

In one experiment with subject A, 250 c. c. of a 10 per cent solution of alcohol was given. (See fig 66.) The ingestion was followed immediately by a definite lowering of the respiratory quotient from 0.85 to 0.80. The general level of the oxygen absorption was about 10 per cent higher after the alcohol, though the effect was somewhat delayed. The pulse-rate varied in its course, being somewhat higher in the hour after the alcohol, then falling sharply when the subject was asleep, rising in the third hour, and remaining at a high level (80 beats and over) for the next 4 hours.

## Discussion of Composite Chart for Mouth Experiments.

A composite chart showing the results of the ingestion of alcohol by mouth in the six experiments is given in figure 67. The quantities of alcohol taken varied from 18.8 to 25 grams. In general, therefore, the amounts taken were slightly lower than those in the rectal experiments with a 7.5 per cent alcohol solution.

*Pulse-rate.*—The average pulse-rate during the preliminary portion of the experiments was between 66 and 67 beats per minute. Immediately after the ingestion of alcohol the average pulse-rate was nearly 70 beats. Presumably this was almost wholly a psychic effect due to the taste of the alcohol in water, for the pulse-rate fell thereafter for a period of 2 hours. It then began to rise, reaching 74 beats at the end of 4 hours, an increase of 7 beats over the preliminary level. Part of this rise was undoubtedly due to the fact that in many of the experiments there was a difference in sleep conditions, as the subject was asleep in the early part of the experiment and awake during the latter part.

*Oxygen absorption.*—The oxygen absorption in the preliminary period was about 245 c. c. Immediately after the ingestion of alcohol by mouth, there was a marked rise, part of which was due to the activity and the psychic effect of taking the alcohol. During the first half hour following the ingestion of alcohol, the oxygen absorption fell rapidly until it reached approximately 235 c. c., thus falling below the preliminary value. It remained at

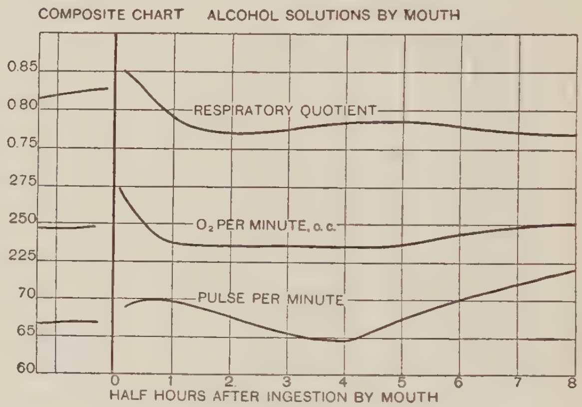



FIG. 67.—Chart showing composite results for measurements of respiratory quotient, oxygen absorption, and pulse-rate in 6 experiments with oral ingestion of 18.8 to 25 grams of alcohol in solutions with varying concentrations. (Mask.)

this level for nearly $2\frac{1}{2}$ hours, then rose slightly until at the end of the experimental period, 4 hours after the ingestion of alcohol, it was slightly higher than the average value during the preliminary period. It is questionable whether this change was due to the alcohol or to the difference in sleep conditions, as in some of the experiments the subject was asleep in the early part of the experiment and awake in the latter part.

*Respiratory quotient.*—The respiratory quotient shows a slightly ascending value during the preliminary period, with an average of about 0.82. Subsequent to the taking of alcohol there was at first a high quotient of 0.85, from which it fell in less than an hour to 0.77, that is, 0.05 below the preliminary value. During the second hour after ingestion the quotient rose slightly, but again fell, even during the period when apparently the subject was awake. This would indicate that the alcohol produced a definite lowering of the respiratory quotient which was present during the entire 4 hours following ingestion by mouth.

## General Conclusions Regarding Experiments with Ingestion of Alcohol by Mouth.

We have, then, a slightly different picture when the alcohol is given by mouth from that when it is given by rectal injection. With alcohol taken by mouth, the effect, when found, is quickly apparent, for in four of the six experiments, there was an immediate fall in the respiratory quotient in the first half hour, while with rectal feeding the fall did not usually take place for an hour and a half, and sometimes more, after the giving of the alcohol.

These experiments were conducted primarily as a comparison series to determine whether there was any difference in the metabolism and pulse-rate when alcohol was introduced by mouth as compared with that introduced by rectum. Unfortunately, the quantity of alcohol used in these experiments was not so large as in a great many of the experiments with rectal injection, there being but one experiment in which the amount introduced was 25 grams.

There were four experiments in the alcohol series in which 400 c. c. of a 5 per cent alcohol solution were injected, and it is thus possible to compare the results of the mouth experiments with those in which a like amount of alcohol was given rectally. On inspecting these two groups we find, first, that the alcohol given by mouth lowered the respiratory quotient more promptly than it did with rectal injection, although the lowering of the respiratory quotient was of about the same order and if anything slightly greater with rectal injection than with ingestion by mouth. As seen from the studies of the alcohol in the urine, the peak of the alcohol concentration was reached about the same time with introduction by mouth or by rectum. Consequently, the lowering of the respiratory quotient was not primarily due to the earlier appearance of an increased concentration in the blood, and there must be a difference in the character of the metabolism or the way in which the metabolism changes are brought about.

The decrease or lowering of the respiratory quotient with ingestion of alcohol by mouth occurred so promptly that it is hardly conceivable that it was due wholly to the maximum concentration of alcohol in the blood. It more likely was due to the initiation of a process in which alcohol takes a part, but with introduction by rectum this process does not begin so promptly as with ingestion by mouth. Whether this lag with rectal introduction is due to an activity of the liver when the material is introduced by mouth and its inactivity when the material is introduced by rectum can not be shown by these experiments, but it may be offered as a hypothesis that this is the cause. On the other hand, with rectal introduction of alcohol, the pulse-rate increased more promptly and to a greater extent than when the alcohol was introduced by mouth; in fact, with 400 c. c. of a 5 per cent solution given by mouth, there was very little increase in the pulse-rate, while, on the contrary, when the material was introduced rectally the increase in the pulse-rate was definite in 3 out of 4 experiments. In the fourth experiment no pulse-rate was taken. We thus see that the action of alcohol upon the metabolism is different, according to whether it is measured by the respiratory exchange or by the pulse-rate. This difference will be discussed further in a comparison of the effects of rectal feeding and mouth feeding in a later section. (See p. 189.)

## RESPIRATORY EXCHANGE WITH RECTAL INJECTION OF DEXTROSE.

In connection with this research, 10 experiments were carried out in which the respiratory exchange was determined in short periods before and after the rectal injection of solutions of dextrose; 7 of the experiments were made in the evening, 2 in the afternoon, and 1 in the morning. The procedure was the same as for the experiments with the solution of sodium chloride and with the alcohol solutions. The sugar used (Kahlbaum's purified dextrose) was weighed out in the quantity desired and dissolved in a 0.6 per cent solution of sodium chloride. In several cases 10 drops of tincture of opium were also added. In 2 experiments, a 5 per cent solution

TABLE 27.—*Statistics of respiratory exchange observations before and after the injection by rectum of a 0.6 per cent solution of sodium chloride containing dextrose.*

| Subject. | Date. | Volume injected. | Weight of dextrose. | Duration of injection. | Periods before dextrose. | | Periods after dextrose. | |
|---|---|---|---|---|---|---|---|---|
| | | | | | No. | Time covered. | No. | Time covered. |
| | 1916. | *c. c.* | *grams.* | *min.* | | *h. min.* | | *h. min.* |
| A | May 4 | 500 | 30 | 94 | 6 | 1 00 | 24 | 4 00 |
| | May 9 | 510 | [a]30 | 88 | 6 | 1 00 | 22 | 4 00 |
| C | May 11 | 510 | 30 | 29 | 6 | 1 00 | 17 | 3 33 |
| D | May 15 | 510 | 30 | 42 | 6 | 1 00 | 21 | 3 59 |
| C | May 13[b] | 510 | [a]30 | 58 | [c]18 | 2 58 | 11 | 2 6 |
| A | Apr. 28 | 1,000 | [a]60 | 254 | 0 | 0 00 | 26 | 5 3 |
| | May 6 | [d]500 | 30 | 102 | 6 | 1 00 | 30 | 5 00 |
| | May 16 | [d]500 | [a]30 | 87 | 0 | 0 00 | 24 | 4 00 |
| | 1917. | | | | | | | |
| | Feb. 22[e] | 520 | [a]30 | 99 | 3 | 1 32 | 12 | 6 1 |
| C | Apr. 17[e] | [f]500 | 30 | 81 | 4 | 2 7 | 8 | 4 14 |

[a] Also 10 drops of tincture of opium.
[b] This experiment was begun 1 hour after the end of an experiment in which 500 c. c. of a 5 p. ct. alcohol solution and 250 c. c. of a 10 p. ct. alcohol solution were injected rectally.
[c] Includes periods before and after injection of alcohol solution on the same day. (See fig. 72.)
[d] The dextrose was dissolved in a 5 per cent alcohol solution instead of in a 0.6 per cent solution of sodium chloride.
[e] These experiments were made with the clinical chamber respiration apparatus. The other dextrose experiments were all made with the gasometer and mask combination. The men were in the lying position in all cases.
[f] The dextrose was dissolved in 500 c. c. of distilled water instead of in a 0.6 per cent solution of sodium chloride.

of alcohol was substituted for the solution of sodium chloride; 8 of the 10 experiments were carried out by means of the mask, valves, gasometer, and gas analysis. The remaining 2 experiments (February 22 and April 17, 1917) were made with the clinical respiration apparatus [1] in the morning, with the subject in the post-absorptive condition, the last meal having been taken the evening before.

A list of the observations, with subject, date, amount of dextrose injected, and the number of periods, is given in table 27. Three subjects, A, C, and D, were employed. The weight of dextrose used was 30 grams in a volume of 500 to 520 c. c., except on April 28, when it was 60 grams in a volume of 1,000 c. c. The time of injection varied from 29 minutes on May 11, 1916,

[1] Benedict and Tompkins: Boston Med. and Surg. Journ., 1916, 174, pp. 857, 898, and 939.

to 254 minutes on April 28, 1916. With one exception, the number of periods before injection ranged between none on April 28 and May 16 and 6 on 5 days. On May 13 the number of periods before injection of the dextrose

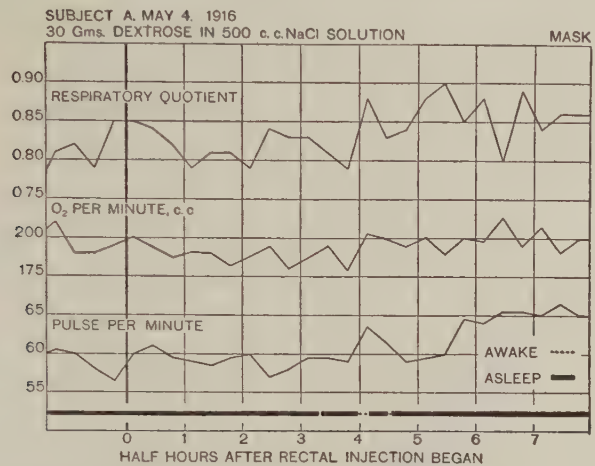



FIG. 68.—Respiratory quotient, oxygen absorption, and pulse-rate of subject A, May 4, 1916, before and after rectal injection of 30 grams of dextrose in 500 c. c. of a 0.6 per cent solution of sodium chloride. (Mask, with continuous observation.)

The horizontal line at the bottom of this and subsequent charts gives a record of sleep, the solid portions indicating when the subject was asleep and the broken portions when the subject was awake.

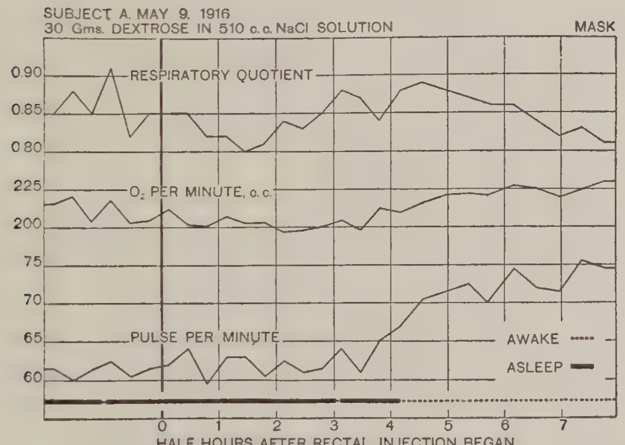



FIG. 69.—Respiratory quotient, oxygen absorption, and pulse-rate of subject A, May 9, 1916, before and after rectal injection of 30 grams of dextrose in 510 c. c. of a 0.6 per cent solution of sodium chloride. (Mask, with continuous observation.)

was 18, but this number includes the periods before and after injection of solutions of alcohol on the same day. The time covered by the preliminary periods varied from 1 hour to 2 hours and 58 minutes. The length of

the individual periods was usually about 10 minutes, except in the 2 experiments with the clinical chamber, in which it was approximately 30 minutes. The number of periods after the injection began varied from 11 to 30 in the experiments with the gasometer method and 10-minute periods, and from 8 to 12 in the experiments with the clinical respiration chamber.

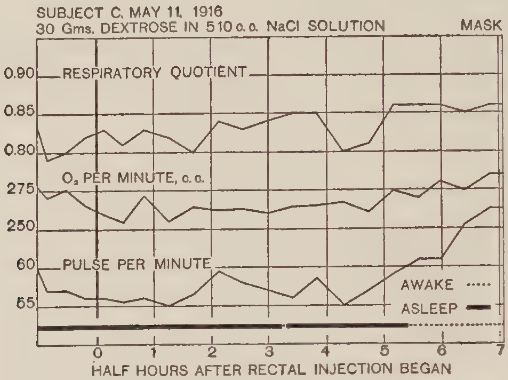



Fig. 70.—Respiratory quotient, oxygen absorption, and pulse-rate of subject C, May 11, 1916, before and after rectal injection of 30 grams of dextrose in 510 c. c. of a 0.6 per cent solution of sodium chloride. (Mask, with continuous observation.)

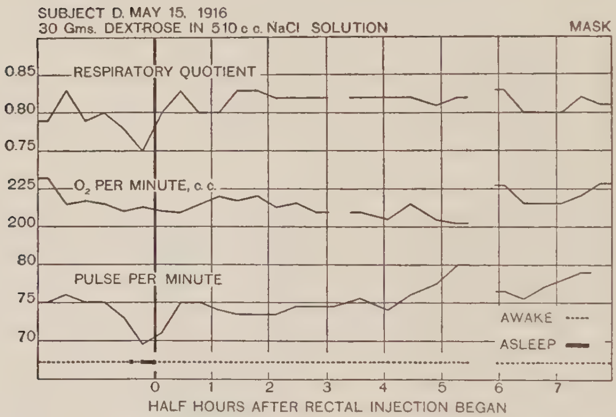



Fig. 71.—Respiratory quotient, oxygen absorption, and pulse-rate of subject D, May 15, 1916, before and after rectal injection of 30 grams of dextrose in 510 c. c. of a solution of sodium chloride. (Mask, with continuous observation.)

The discussion of the results of these observations follows, the method of treatment being the same as that for the preceding series, with charts (figs. 68 to 77) showing the respiratory quotient, oxygen absorption, and pulse-rate for each experiment. The determinations of the absorption of the dextrose have already been considered. (See pp. 30 to 33.)

RESULTS OF MEASUREMENTS BEFORE RECTAL INJECTION.

With subject A, on May 6, the last food was at 8 a. m., while the first period of the experiment was at $1^h$ $39^m$ p. m. On May 4 and May 9 the

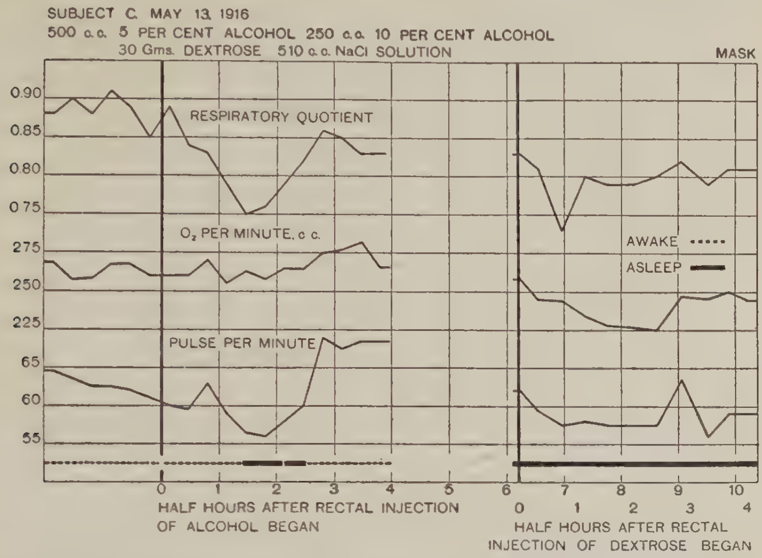



FIG. 72.—Respiratory quotient, oxygen absorption, and pulse-rate of subject C, May 13, 1916, before and after rectal injection of 500 c. c. of a 5 per cent alcohol solution and 250 c. c. of a 10 per cent alcohol solution, and after a second injection of 30 grams of dextrose in 510 c. c. of a 0.6 per cent solution of sodium chloride. (Mask, with continuous observation.)

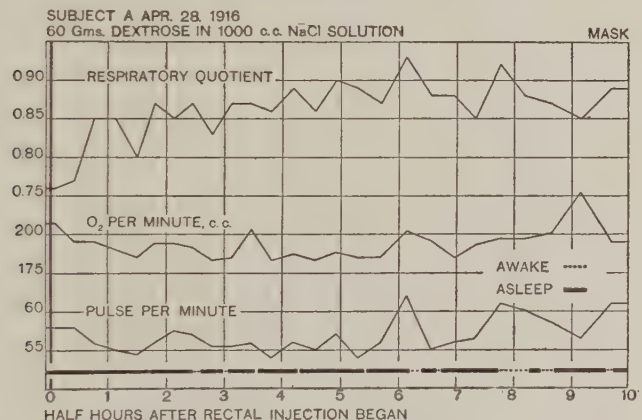



FIG. 73.—Respiratory quotient, oxygen absorption, and pulse-rate of subject A, April 28, 1916, after rectal injection of 60 grams of dextrose in 1,000 c. c. of a 0.6 per cent solution of sodium chloride. (Mask, with continuous observation.)

last food was at $1^h$ $30^m$ p. m., while the first periods were at $6^h$ $29^m$ and $5^h$ $05^m$ p. m., respectively. The two experiments with A on May 16 and April 28 were carried out in the early part of the evening, with food presumably at noon, although no record was made at the time.

With C on May 11, the last food was at 1$^h$ 30$^m$ p. m. and the first period began at 5$^h$ 56$^m$ p m. On May 13 the subject had at 8 a. m. a cupful of coffee with 2 teaspoonfuls of sugar; the first period began at

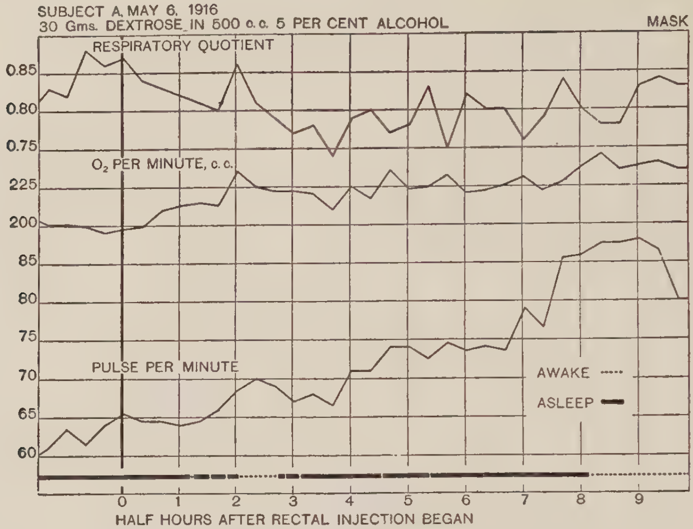



FIG. 74.—Respiratory quotient, oxygen absorption, and pulse-rate of subject A, May 6, 1916, before and after rectal injection of 30 grams of dextrose in 500 c. c. of a 5 per cent alcohol solution. (Mask, with continuous observation.)

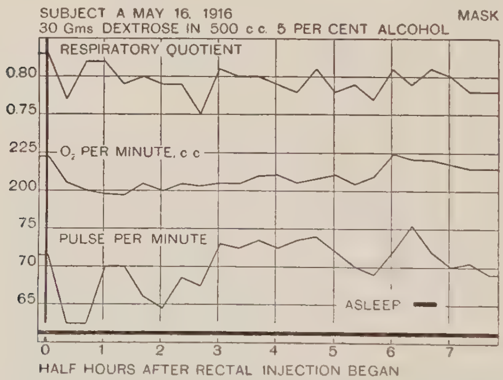



FIG. 75.—Respiratory quotient, oxygen absorption, and pulse-rate of subject A, May 16, 1916, after rectal injection of 30 grams of dextrose in 500 c. c. of a 5 per cent alcohol solution. (Mask, with continuous observation.)

9$^h$ 50$^m$ a. m. With subject D, on May 15, the last food was at 8 a. m. and the first period began at 2$^h$ 20$^m$ p. m.

### PULSE-RATE.

The preliminary pulse-rates for subject A in the two experiments on May 4 and 9 were 59 and 61 beats per minute, respectively. On May 6, 1916, and

February 22, 1917, they averaged 63 beats for both experiments. In the latter experiment the subject was in the post-absorptive condition. There were no preliminary periods on May 16 and on April 28. With subject C, the preliminary pulse-rate on May 11 was 57 beats and on May 13 and April

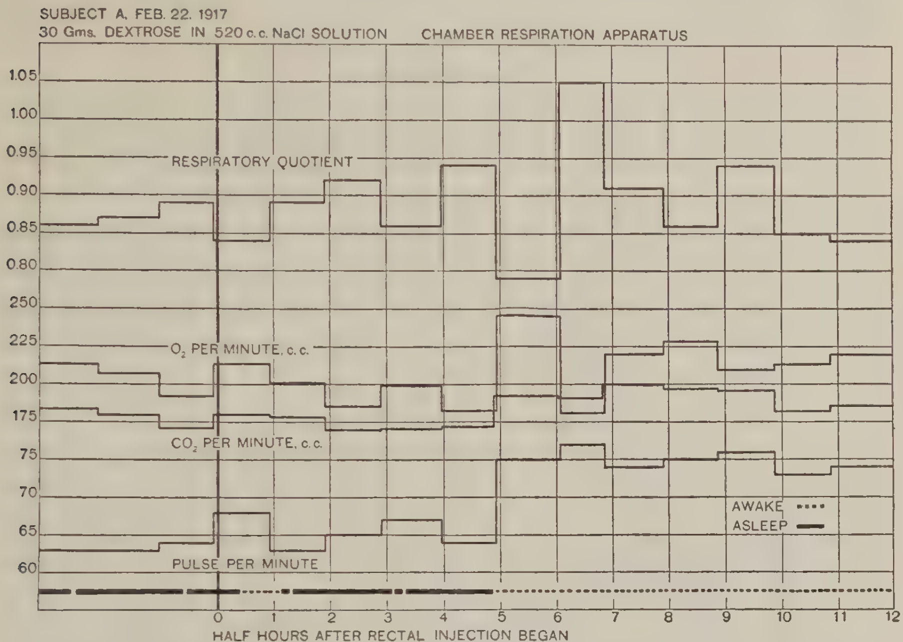



**Fig. 76.**—Respiratory quotient, oxygen absorption, carbon-dioxide elimination, and pulse-rate of subject A, February 22, 1917, before and after rectal injection of 30 grams of dextrose in 520 c. c. of a 0.6 per cent solution of sodium chloride. (Chamber respiration apparatus.)

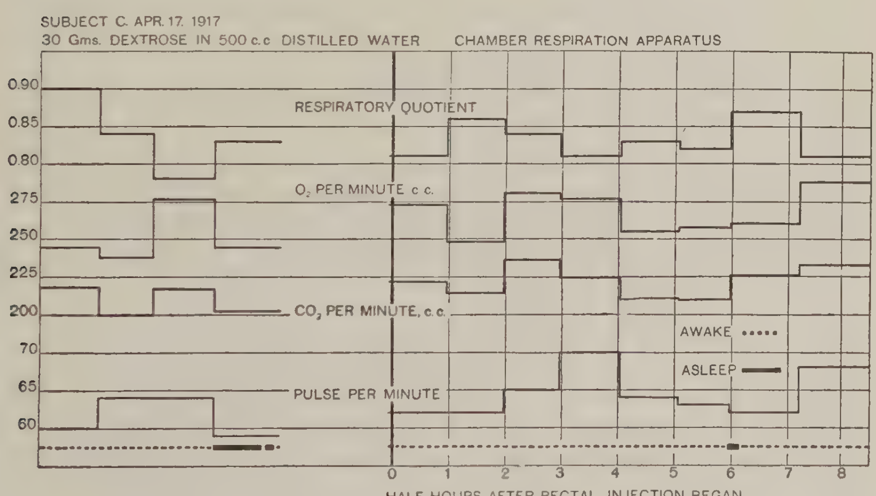



**Fig. 77.**—Respiratory quotient, oxygen absorption, carbon-dioxide elimination, and pulse-rate of subject C, April 17, 1917, before and after rectal injection of 30 grams of dextrose in 500 c. c. of distilled water. (Chamber respiration apparatus.)

17 it was 63 beats. On April 17, C was in a post-absorptive condition. With subject D, the average pulse-rate for the six periods before the injection took place was 74 beats. The pulse-rates, therefore, for both subjects A and C were near their basal pulse-rates, which for subject A was 64 beats and for subject C 65 beats. (See table 1, p. 22.) No basal pulse-rate is available for subject D.

### Oxygen Absorption.

The average oxygen absorption before injection of subject A on May 4 was 196 c. c. per minute, on May 6, 198 c. c., and on May 9, 211 c. c. On February 22, 1917, when he was in a post-absorptive condition, it was 204 c. c. per minute. All these values closely approximate his basal absorption of 206 c. c., given in table 1, page 22. With subject C, on May 11, the preliminary average was 271 c. c. per minute, on May 13, 261 c. c., and on April 17, 1917, 251 c. c. These values were somewhat lower than the *average* basal value for this subject of 285 c. c. (See table 1.) With subject D, the average absorption before injection was 215 c. c. per minute, which is a somewhat low average for this individual.

### Respiratory Quotient.

The preliminary respiratory quotients in four of these experiments were somewhat higher than in the majority of experiments heretofore considered. With subject A, on May 4, the quotient was 0.82, on May 6, 0.85, and on May 9, 0.86. On February 22 (the post-absorptive day) it was 0.87. With subject C, the respiratory quotients on May 11 and April 17 were 0.80 and 0.84, respectively. On May 13 it was high, being 0.89. This was the experiment in which C had a cupful of coffee and 2 teaspoonfuls of sugar at 8 a. m. and the experiment began at about 10 a. m. The respiratory quotient before injection with subject D on May 15 was 0.79. These quotients were, therefore, not entirely ideal for the study of a superimposed condition, which would tend to raise the respiratory quotient, namely, the ingestion of dextrose.

## Results of Measurements After Rectal Injection of Dextrose (Gasometer Method).

In the first four experiments considered in this section, 30 grams of dextrose were given in approximately 500 c. c. of a solution of sodium chloride. Two of these experiments were with subject A, one with subject C, and one with subject D. In the two experiments with subject A, there was an indication of a marked rise in the respiratory quotient. In the experiment on May 4, the rise began about 2 hours after the beginning of the injection, and in the experiment on May 9 this rise was a little earlier, i. e., $1\frac{1}{2}$ to 2 hours after the dextrose, with a tendency to a decline afterward. In the experiment with subject C (May 11), there was some indication of a rise in the quotient about 1 hour after the solution was given. With subject D there was very little indication of any real change in the quotient. In three experiments out of four, therefore, with 30 grams of dextrose and 500 c. c. of a sodium-chloride solution, the respiratory quotient rose in 1 to 2 hours after the flow of the solution began. The time of change is comparable with that indicated in the experiments with rectal introduction of alcohol.

The oxygen absorption in the two experiments with subject A shows a slight tendency to increase within 2 hours after the introduction of the solution commenced. The increase on May 9 was somewhat more positive than that on May 4, but this increase is coincident with the awakening of the subject from sleep. In the experiment with subject C there was also a slight change in the oxygen absorption in the last hour of the experiment, but this again is coincident with the wakening of the subject. In the experiment with subject D there was no evidence of a change in the oxygen absorption until about $3\frac{1}{2}$ hours after the beginning of the injection, and this rise occurred immediately after the subject was obliged to urinate.

The pulse-rates in the four experiments tended to rise, also, but in at least two of the experiments this change occurred when the subject awakened. The rise in the pulse-rate in the experiment with subject A on May 4 was, however, independent of such change in conditions of sleep.

Summarizing the results of these four experiments, we find a positive rise in the respiratory quotient, a positive increase in the pulse-rate occurring within 3 hours, and some increase in the oxygen absorption. This amount of dextrose is very small in comparison with the quantities usually given by mouth in studies of carbohydrates in which 50, 75, and even 100 grams have ordinarily been ingested. It is surprising, therefore, that so small an amount of dextrose as was given in the experiments here discussed should produce any material change in either the respiratory quotient or the oxygen absorption, and especially in the pulse-rate. The proportion of the total metabolism which was supplied by the dextrose thus utilized and the percentage effect upon the total metabolism are considered later in the general discussion of results. (See p. 186.)

One experiment was made with subject A, on April 28, 1916, in which 60 grams of dextrose were given in 1,000 c. c. of a solution of sodium chloride in the course of $4\frac{1}{4}$ hours. The introduction of this amount resulted in a very positive and gradual increase in the respiratory quotient in the dextrose periods, which began $1\frac{1}{2}$ hours after the flow of the solution started, and although somewhat irregular in its course, continued throughout the rest of the experiment ($3\frac{1}{2}$ hours). The pulse-rate, on the other hand, did not change materially. While the oxygen absorption was somewhat irregular from period to period, apparently it was likewise uninfluenced by the carbohydrate.

There were two experiments, both with subject A, in which 30 grams of dextrose were given in 500 c. c. of a 5 per cent alcohol solution. The object of these two experiments was to determine which material would predominate in the metabolism as shown by the respiratory quotient when alcohol and dextrose were given simultaneously. In the experiment on May 6 there was a noticeable decrease in the respiratory quotient which began shortly after the injection commenced and reached its lowest level near the end of the second hour. The average respiratory quotient before the injection commenced was 0.86; after the injection it fell on the average as low as 0.77. It might appear that part of this fall was due to the height of the initial respiratory quotient. This may have been true, but the entire fall can not be ascribed to a natural lowering of the respiratory quotient from the initial high value. In all probability, the alcohol was effective in lowering the respiratory quotient, in spite of the fact that dextrose was

simultaneously given. In other words, the alcohol was utilized rather than the dextrose, or enough alcohol was made use of to offset the increase due to utilization of dextrose.

In the experiment on May 16 there were no preliminary periods; hence we have no data as to the initial respiratory quotient. The general level of the quotient was not altered during the experiment, so that in this case there was neither an increase due to the utilization of dextrose nor a fall due to the utilization of alcohol, or if such use took place, the two substances counterbalanced one another in their effect.

The oxygen absorption in the experiment on May 6 began to increase within the first hour and rose to a level 25 c. c. higher than that for the preliminary period, and continued on this level for 2½ hours. At the end of the fourth hour the oxygen values rose still higher. At this time, however, the subject woke up and remained awake for the rest of the experiment. In the experiment on May 16, the general level of the oxygen absorption remained practically unaltered for about 3 hours after the beginning of the injection. In the fourth hour after injection, it was increased materially from 10 to 15 c. c. per minute.

The pulse-rate with the subject on May 6 increased from a preliminary average value of 63 beats to a value of 74 beats in the course of 3 hours. When the subject awoke at the end of the fourth hour, it changed from the level of 74 beats to one of over 85 beats. In the experiment on May 16, the pulse-rate was very irregular for the first 1½ hours after injection and the general level was below 70 beats. During the next hour it averaged 73 beats and the general level for the last 2½ hours of the experiment was higher than the 1½ hours preceding. There was thus an increase in the pulse-rate which is in line with the other experiments and presumably due chiefly to the influence of alcohol. In the experiment on May 6, it would appear as though both alcohol and dextrose influenced the results.

There was an experiment on May 13 with subject C, which was in reality composed of two parts. In the first section of the experiment, after the preliminary period, 500 c. c. of a 5 per cent alcohol solution, and 250 c. c. of a 10 per cent alcohol solution, or 50 grams of alcohol in all, were given to the subject over a period of 2 hours. There was then a rest of about an hour. At the end of the rest period he was given 30 grams of dextrose in 500 c. c. of 0.6 per cent sodium-chloride solution. The object of this experiment was to determine when the effect of the rectal injection of alcohol was ended and whether dextrose, injected later than the alcohol, would alter the metabolism.

The pulse-rate indicated the greatest change, being markedly depressed by a period of sleep which occurred in the second half hour, and falling from 63 to 56 beats. When the subject awoke, the pulse-rate rose considerably above the pulse-rate in the preliminary periods, or 68 beats as compared with 63 beats. After the period of rest following the alcohol section of the experiment, the pulse-rate again fell to a generally low level and remained there with some variation throughout the rest of the experiment.

The oxygen absorption was slightly increased in the second hour after the beginning of the alcohol injection, but in the period during which the dextrose solution was given, the oxygen absorption was materially lowered. Therefore the dextrose injection did not produce a stimulating effect upon the total metabolism.

The average respiratory quotient of 0.88 in the preliminary period was somewhat high upon which to superimpose the effect of alcohol. As would naturally be expected, the quotient fell from this level, dropping to 0.75 during a period of sleep in the second half hour after injection. This fall was presumably due to both alcohol and sleep. When the subject was awake in the last half hour of the alcohol experiment the quotient was slightly lower than in the preliminary period. During the period of time beginning 3 hours after the injection of alcohol commenced, when dextrose was injected, the respiratory quotient was on a generally lower level than at any time preceding it, with apparently no influence of dextrose upon the respiratory quotient. In general, it would appear as if the main influence was due to alcohol, although the fall was not so large as would be expected with this large amount of alcohol (50 grams).

### Results of Measurements After Rectal Injection of Dextrose (Chamber Method).

The two experiments with the clinical respiration chamber (February 22 and April 17) indicate some increase in pulse-rate which is caused in part by the awakening of the subject, but also due in part to the rectal injection of dextrose. In both the experiments the respiratory quotient shows slight increases (0.02 to 0.05), occurring 2 to 3 hours after the injection. The oxygen absorption in one experiment, that with A on February 22, rose after 3 hours and in the other immediately after injection.

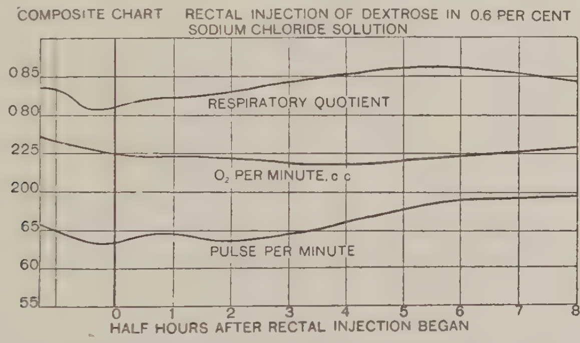



Fig. 78.—Chart showing composite results for measurements of respiratory quotient, oxygen absorption, and pulse-rate in 9 experiments with rectal injection of 30 grams of dextrose in solution. (Mask or clinical respiration chamber.)

### Discussion of Composite Chart.

The composite chart for the dextrose series is given in figure 78. This chart includes all of the experiments with 30 grams of dextrose made by the two methods.

*Pulse-rate.*—The pulse-rate during the preliminary period was nearly the same as the composite for the experiments when alcohol was taken by mouth. (See fig. 67, p. 138.) In the pre-injection period it varied from 66 to 63 beats per minute. During the first hour after injection there was little alteration, but at the end of the first hour the pulse-rate began to rise and rose gradually until during the fourth hour it was nearly 70 beats per minute. There was thus a definite rise in the average pulse-rate during the observations, due to the injection of the dextrose solution.

*Oxygen absorption.*—The oxygen absorption in the preliminary 40 minutes fell from 235 c. c. to 225 c. c., and continued to decrease for 1½ hours after the dextrose injection began. It remained unaltered for about an hour, then rose again, but the average absorption did not at any time rise to the average value for the preliminary period. It would appear that dextrose exercised slight, if any, effect upon the average oxygen absorption, although some of the individual experiments did show some increase.

*Respiratory quotient.*—During the preliminary period the respiratory quotient fell markedly. After the injection it rose again, although during the first hour it did not reach the preliminary level. This increase continued until in the third hour after injection it was considerably above the preliminary value, being 0.86 as compared with 0.81. This level was maintained until nearly the end of the experiment, that is, 4 hours after injection. Whether this increase was caused by the dextrose injection or whether such injection favored an increased utilization of carbohydrate is not known. The rise of the respiratory quotient definitely indicates an increase in the metabolism of carbohydrates.

### General Conclusions Regarding Respiratory Exchange with Rectal Introduction of Dextrose.

The rectal injection of 30 grams of dextrose in 500 c. c. of a sodium-chloride solution caused a rise in pulse-rate of 5 beats per minute in 2 to 3 hours after injection. It also increased the respiratory quotient 0.02 to 0.05 in 2 to 3 hours after the injection began.

In the majority of the experiments the oxygen consumption increased slightly, this increase taking place either immediately or within 2 hours after the injection began. When the dextrose was given in a 5 per cent alcohol solution there was no increase in the respiratory quotient, but there was an increase in both pulse-rate and oxygen consumption. This effect is considered to be due more especially to the effect of alcohol than to the injection of the dextrose solution. Even on the day when alcohol was given in the morning and dextrose solution in the afternoon, there was no apparent effect upon the metabolism due to the introduction of the dextrose.

The increase in the respiratory quotient after the giving of dextrose by rectum must indicate an increase in utilization of the dextrose injected or else bring about a condition in which there is an increase in the proportion of carbohydrate in the metabolism. The amount of carbohydrate which is metabolized under these conditions is considered in a later section in the theoretical discussion of results. (See p. 186.)

## RESPIRATORY EXCHANGE WITH RECTAL INJECTION OF LEVULOSE.

A series of experiments to determine the effect of the rectal injection of levulose upon the respiratory exchange, with particular reference to its effect upon the respiratory quotient and the oxygen absorption, was carried out in the early part of 1916, and, in fact, before the series with dextrose just discussed.

The subjects were the same as those used in the study with dextrose, viz, A, C, and D. Kahlbaum's commercial grade of levulose was

employed.[1] The method of preparing the solution and the experimental procedure were likewise the same as in the dextrose experiments.

The number and character of the experiments are shown in table 28; the graphic records are given in figures 79 to 88. The levulose was in all cases administered in a 0.6 per cent solution of sodium chloride. In 4 experiments 25 grams of levulose were given in a volume of 500 c. c., in 1 experiment 37.5 grams in a volume of 750 c. c., in 2 experiments 50 grams in a volume of 1,000 c. c., and in 3 experiments the same amount in a volume of 500 c. c. The duration of the injection varied from 19 minutes to 129 minutes. The number of periods in which the respiratory exchange was measured before injection varied from 4 to 9 and the time covered by these periods from 40 minutes to 1 hour and 30 minutes. The number of periods after the injection began varied from 13 to 26 and the time covered from 2 hours and 9 minutes to 4 hours and 20 minutes.

TABLE 28.—*Statistics of respiratory exchange observations before and after the injection by rectum of 0.6 per cent solution of sodium chloride containing levulose.*

| Subject. | Date.[a] | Volume injected. | Weight of levulose. | Duration of injection. | Periods before levulose. | | Periods after levulose. | |
|---|---|---|---|---|---|---|---|---|
| | | | | | No. | Time covered. | No. | Time covered. |
| | 1916. | *c. c.* | *grams.* | *min.* | | *h. min.* | | *h. min.* |
| C. | Feb. 1 | 500 | 25.0 | 95 | 7 | 1 10 | 19 | 3 10 |
| | Feb. 7 | 500 | [b] 25.0 | 19 | 6 | 1 00 | 17 | 2 50 |
| D. | Feb. 3 | 500 | 25.0 | 62 | 6 | 1 00 | 17 | 2 50 |
| | Feb. 11 | 500 | [b] 25.0 | 30 | 9 | 1 24 | 16 | 2 39 |
| C. | Feb. 15 | 750 | [b] 37.5 | 57 | 4 | 0 40 | 16 | 2 40 |
| | Jan. 25 | 1,000 | [b] 50.0 | 99 | 6 | 1 00 | 20 | 3 21 |
| D. | Jan. 28 | 1,000 | 50.0 | 129 | 9 | 1 30 | 13 | 2 9 |
| A. | Jan. 15 | 500 | 50.0 | 29 | 7 | 1 10 | 15 | 2 38 |
| | Jan. 18 | 500 | 50.0 | 95 | 7 | 1 11 | 26 | 4 20 |
| C. | Jan. 12 | 500 | 50.0 | 54 | 6 | 1 00 | 19 | 3 34 |

[a] All of the levulose experiments were made with the gasometer and mask combination.
[b] Also 5 to 6 drops of tincture of opium.

## RESULTS OF MEASUREMENTS BEFORE RECTAL INJECTION.

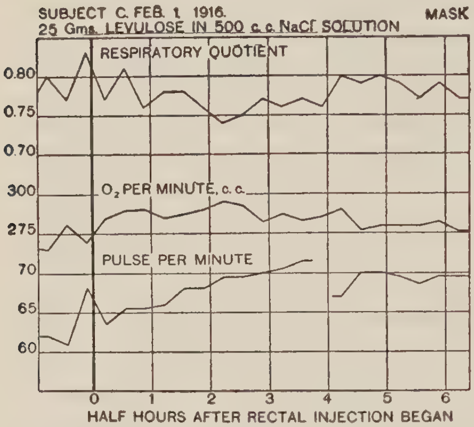
The conditions under which these experiments were carried out were practically the same as in the previous groups. All but two observations began between 5 and 6 p. m. The experiment with A, January 15, began at $2^h\ 30^m$ p. m., and on January 18 at $3^h\ 20^m$ p. m. No food was taken after $8^h\ 15^m$ a. m. on any day. On January 15 and January 18, the first period began within 10 minutes after the subject lay down, and on January 12 in 20 minutes. In all the other experiments there was at least a half hour of preliminary rest before the first period recorded in the curves.

### PULSE-RATE.

The average preliminary pulse-rate for subject A was 60 beats on January 15 and 70 beats on January 18, as compared with the basal pulse-rate of

[1] The levulose was the same as that used in a previous study by Joslin (Joslin: Carnegie Inst. Wash. Pub. No. 323, 1923, p. 213), and contained, according to previous analysis, 4.8 per cent of moisture. In reporting the results of both researches, however, the moisture in the levulose has not been taken into consideration.

64 beats reported for this subject in table 1, page 22. The averages for C ranged before injection from 62 beats on February 7 to 66 beats on January 12. His basal pulse as given in table 1, page 22, was 65 beats. The average rates in the preliminary periods with D ranged from 71 to 80 beats.

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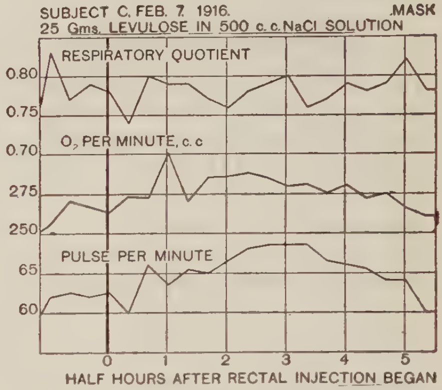


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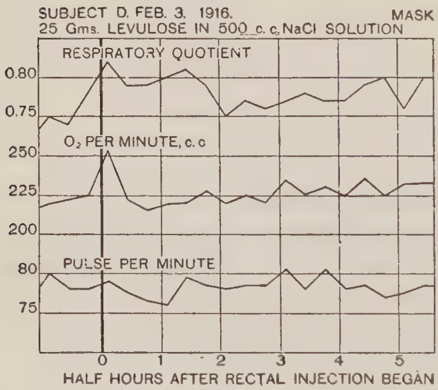
FIG. 79.—Respiratory quotient, oxygen absorption, and pulse-rate of subject C, February 1, 1916, before and after rectal injection of 25 grams of levulose in 500 c. c. of a 0.6 per cent solution of sodium chloride. (Mask, with continuous observation.)

FIG. 80.—Respiratory quotient, oxygen absorption, and pulse-rate of subject C, February 7, 1916, before and after rectal injection of 25 grams of levulose in 500 c. c. of a 0.6 per cent solution of sodium chloride. (Mask, with continuous observation.)

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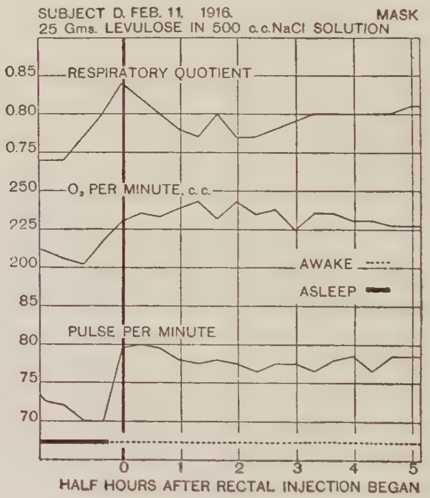


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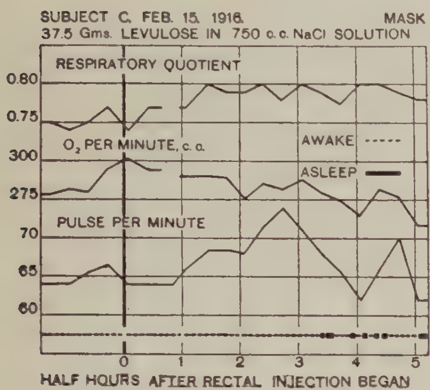
FIG. 81.—Respiratory quotient, oxygen absorption, and pulse-rate of subject D, February 3, 1916, before and after rectal injection of 25 grams of levulose in 500 c. c. of a 0.6 per cent solution of sodium chloride. (Mask, with continuous observation.)

FIG. 82.—Respiratory quotient, oxygen absorption, and pulse-rate of subject D, February 11, 1916, before and after rectal injection of 25 grams of levulose in 500 c. c. of a 0.6 per cent solution of sodium chloride. (Mask, with continuous observation.)

The horizontal line at the bottom of this and subsequent charts gives a record of sleep, the solid portions indicating when the subject was asleep, and the broken portions when he was awake.

### Oxygen Absorption.

The average oxygen absorption before injection for A was 201 c. c. on January 15 and 223 c. c. on January 18. As his basal oxygen consumption

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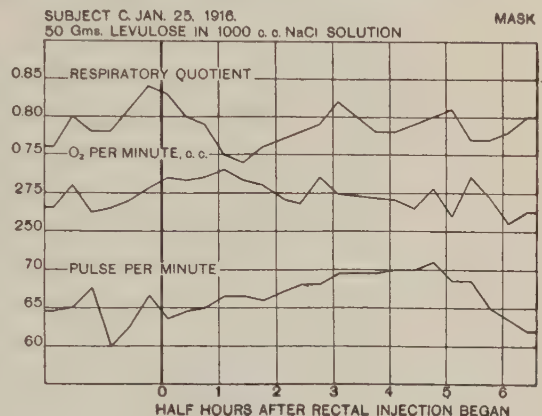


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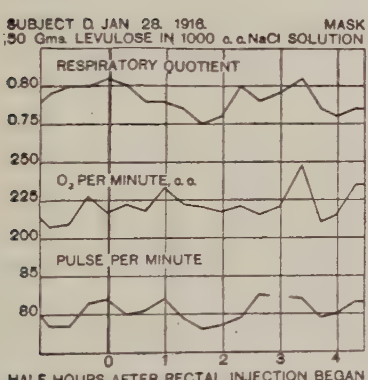
Fig. 83.—Respiratory quotient, oxygen absorption, and pulse-rate of subject C, February 15, 1916, before and after rectal injection of 37.5 grams of levulose in 750 c. c. of a 0.6 per cent solution of sodium chloride. (Mask, with continuous observation.)

Fig. 84.—Respiratory quotient, oxygen absorption, and pulse-rate of subject C, January 25, 1916, before and after rectal injection of 50 grams of levulose in 1,000 c. c. of a 0.6 per cent solution of sodium chloride. (Mask, with continuous observation.)

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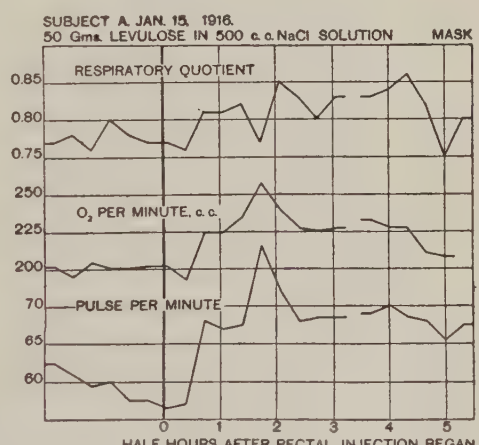


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Fig. 85.—Respiratory quotient, oxygen absorption, and pulse-rate of subject D, January 28, 1916, before and after rectal injection of 50 grams of levulose in 1,000 c. c. of a 0.6 per cent solution of sodium chloride. (Mask, with continuous observation.)

Fig. 86.—Respiratory quotient, oxygen absorption, and pulse-rate of subject A, January 15, 1916, before and after rectal injection of 50 grams of levulose in 500 c. c. of a 0.6 per cent solution of sodium chloride. (Mask, with continuous observation.)

was 206 c. c., the latter value is somewhat high for this subject. He had a slight cold on the evening of January 18. The preliminary values for C ranged from 265 to 286 c. c. His basal oxygen absorption was 285 c. c. The

preliminary oxygen data for D were on February 11, 209 c. c.; on February 3, 222 c. c.; and on January 28, 215 c. c.

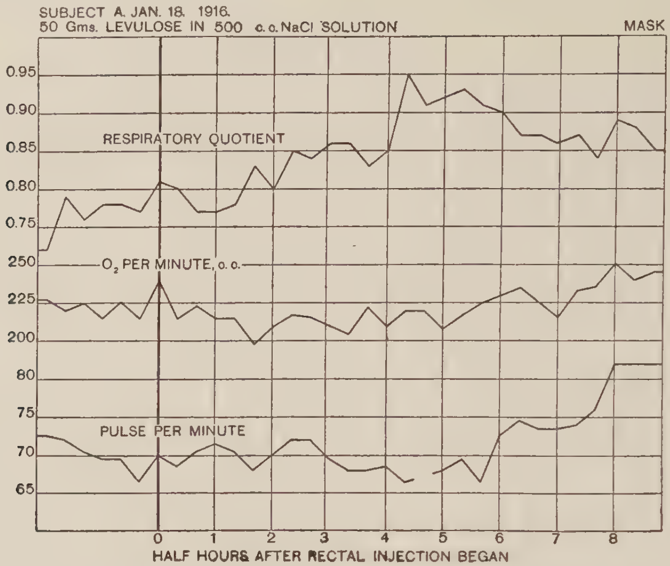


FIG. 87.—Respiratory quotient, oxygen absorption, and pulse-rate of subject A, January 18, 1916, before and after rectal injection of 50 grams of levulose in 500 c. c. of a 0.6 per cent solution of sodium chloride. (Mask, with continuous observation.)

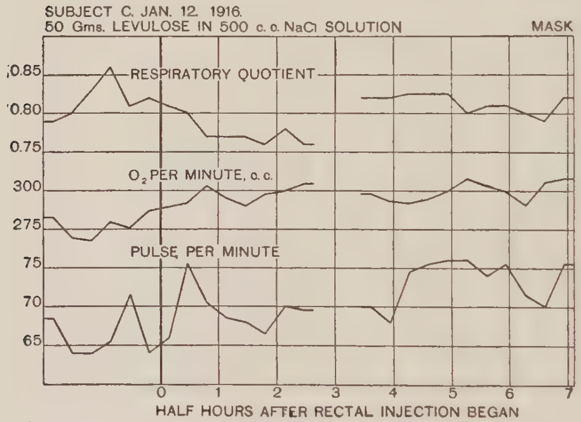


FIG. 88.—Respiratory quotient, oxygen absorption, and pulse-rate of subject C, January 12, 1916, before and after rectal injection of 50 grams of levulose in 500 c. c. of a 0.6 per cent solution of sodium chloride. (Mask, with continuous observation.)

### RESPIRATORY QUOTIENT.

The respiratory quotients for A in the preliminary periods were 0.78 on January 15 and 0.77 on January 18. Those for C ranged from 0.75 on February 15 to 0.82 on January 12. The values for D were 0.80 on Janu-

ary 28 and 0.76 on February 3 and February 11. The range for all the averages of pulse-rate, oxygen absorption, and respiratory quotient in the pre-injection periods were well within the range of results obtained in the basal metabolism measurements, with the exception of those with A on January 18, in which the pulse-rate (70 beats) and oxygen absorption (223 c. c.) were higher than usual.

### Results of Measurements After Rectal Injection of Levulose.

The results of these studies of the respiratory exchange after the rectal injection of a levulose solution are not readily interpreted, as they were comparatively few in number and the conditions varied somewhat. A complete record of the amount of sleep or drowsiness in the experiments was also lacking. While in a number of the observations the introduction of the solution produced no subjective effects, in others the men had cramps and peristaltic movements which may have had a relation to the changes which followed the injection.

In the first four experiments, those with the introduction of 25 grams of levulose in 500 c. c. of a 0.6 per cent solution of sodium chloride, no cramps or peristaltic movements were reported. In the experiment with subject C on February 15, 1916, when 37.5 grams were given in a volume of 750 c. c., there was some pain when the final flushing of the rectum and colon was given. In an experiment with 50 grams of levulose in a volume of 1,000 c. c., the same subject reported a few peristaltic movements near the end of the experiment, and subject D, with a like injection, suffered from cramps for most of the experimental period. When 50 grams of levulose were given in a volume of 500 c. c., subject A on January 15 reported an intense desire to defecate during the experiment, and on January 12 subject C had some peristaltic movement. Subject A on January 18 complained that the solution was administered too rapidly, although it was given more slowly than usual; also that he suffered from cramps during the last hour of the observations.

Owing to the absence of sleep records in many of the experiments, it is not easy to discriminate between the effect of levulose upon the pulse-rate and the effect of sleep. That the pulse-rate was definitely affected by sleep is particularly evident in the experiment with subject D on February 11, for this subject has normally a very high pulse-rate when he is awake. There are, however, some indications that the pulse-rate was raised by the injection of the levulose solution, expecially in the experiments with subject C, when the pulse-rate in every instance rose within 1 to $1\frac{1}{2}$ hours after the beginning of the injection, and was higher at this time than in the first hour after the injection commenced; the comparison is therefore not dependent upon the values for the preliminary period. This change occurred even in the experiments with 25 grams of levulose in which there were no cramps or peristaltic movements.

In the four experiments with 25 grams of levulose and a volume of 500 c. c., there was very little indication of the effect of the injection upon the respiratory quotient, except possibly in the experiment with subject D on February 11 in the fourth half hour after the injection began, when there was an increase of about 0.03. The absorption of the levulose in these four experiments was smaller than that in the other experiments with 37.5 and 50

grams of levulose, varying from 16.2 grams to 21.8 grams. (See table 6, p. 35.)

In the single experiment with 37.5 grams and a volume of 750 c. c., in which there was an apparent absorption of 35.8 grams, the respiratory quotient changed to a higher level during the second half hour after the beginning of the injection, and this level was maintained throughout the rest of the experiment, although the subject was slightly drowsy near the end.

In the two experiments on January 25 and 28 with 50 grams of levulose and a volume of 1,000 c. c., there was apparently no change in the quotients due to levulose. There were cramps in both experiments and a large absorption of levulose, i. e., 33 and 25.9 grams, respectively.

In the three experiments with 50 grams and a volume of 500 c. c., the most marked change was found with subject A on January 18, when the average quotient rose from 0.78 to 0.95, and there was an apparent absorption of 100 per cent of the levulose. It will be remembered that on this day the subject complained of cramps, especially during the last hour, though the maximum quotient did not occur at this time. The emotional disturbance due to cramps may have caused an increase in respiration, and consequently some excessive elimination of carbon dioxide, i. e., a "washing-out," and thus have raised the respiratory quotient. One must bear this in mind when interpreting the results.

In the experiment with the same subject on January 15, the effect was somewhat complicated by the irregularity of respiration due to coughing. There may have been here, also, a slight increase in ventilation as a result of the coughing, with a consequent increase in elimination of carbon dioxide which would raise the respiratory quotient. There was in this experiment a definite rise in the respiratory quotient.

The duration of the experiment seemed to bear no relation to the effect upon the respiratory quotient, as the observations after the beginning of the injection varied from 2 hours and 9 minutes to 4 hours and 20 minutes. Only in the longest observation was there much of a change in the quotient after 2 hours. We thus see that but a single experiment (that with subject A on January 18) indicated a considerable increase in the respiratory quotient due to the rectal injection of levulose, and the absorption of the sugar in this case was practically 100 per cent. Even in this experiment there was the complicating factor of cramps.

The oxygen absorption in most of the experiments gives generally negative evidence as to the influence of the levulose injection. While there were marked variations in this factor, they were doubtless due more especially to momentary excitement or to drowsiness and sleep. The influence of the latter is definitely shown in the experiment with subject D on February 11 and to some extent in the experiment with subject C on February 15. The marked variations in the experiment with subject A on January 15 resulted from the uneven respiration during periods of coughing.

## Discussion of Composite Chart, and Conclusions.

A composite chart for the levulose experiments is given in figure 89, and includes all the experiments which were made with levulose, i. e., those with both 5 per cent and 10 per cent solutions containing 25 to 50 grams of levulose.

*Pulse-rate.*—The curve for the pulse-rate rises slightly during the first 1½ hours after the injection and then falls during the fourth hour nearly to the preliminary value. The rise in the pulse-rate was therefore of short duration and not very marked.

*Oxygen absorption.*—In the oxygen curve there is a slight rise which begins immediately, continues throughout the preliminary period, and practically ceases by the end of the first half hour after injection. It is probable that the levulose had no share in increasing the oxygen absorption in this first half hour after the injection.

*Respiratory quotient.*—The course of the respiratory quotient is somewhat peculiar in that there is a rise during the preliminary period nearly to 0.80 from 0.77. It then drops during the first hour after injection almost to the level at the beginning of the preliminary period, and subsequently rises until, during the third hour after injection, it averages 0.83. This is about 0.05 above the lowest quotient during the hour after injection and the lowest point before injection. This average is influenced to some extent by one or two experiments in which there was a marked rise in the respiratory quotient.

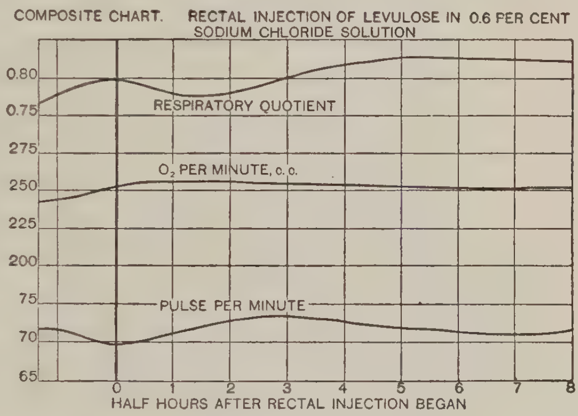


FIG. 89.—Chart showing composite results for measurements of respiratory quotient, oxygen absorption, and pulse-rate in 10 experiments with rectal injection of 25 to 50 grams of levulose in 5 and 10 per cent solutions. (Mask.)

In general, therefore, we may state that the injection of 25 to 50 grams of levulose in solution caused only a slight increase in the respiratory quotient in the majority of cases; that there was no positive effect upon the oxygen consumption; and that the levulose evidently increased the pulse-rate somewhat in individual cases.

## RESPIRATORY EXCHANGE WITH ORAL INGESTION OF SUGARS.

The respiratory exchange with man after the ingestion by mouth of dextrose or levulose has been studied by Durig,[1] Benedict and Carpenter,[2] and Higgins,[3] using 100-gram quantities. These investigators found almost immediate and striking increases in the respiratory quotient and the two former found increases in the metabolism after the ingestion of levulose.

[1] Tögel, Brezina, and Durig: Biochem. Zeitschr., 1913, 50, p. 296.
[2] Benedict and Carpenter: Carnegie Inst. Wash. Pub. No. 261, 1918, p. 171.
[3] Higgins: Am. Jour. Physiol., 1916, 41, p. 258.

The rise both in quotient and total metabolism was less marked after the ingestion of dextrose and did not appear so promptly as with levulose. It was planned in this research to include a series of experiments with oral introduction of levulose and dextrose, using the same quantities and dilutions as in the rectal feeding experiments, these being much smaller than those usually employed for mouth experiments. Only two observations were completed under these conditions, i. e., one each with dextrose and levulose. These are reported here, and while we must not draw fixed conclusions from single experiments, the results are quite in line with previous work on dextrose and levulose and therefore can serve as a basis of contrast with results obtained in rectal feeding.

*Subject C, April 14, 1917.*—Ingestion by mouth, 30 grams dextrose in 500 c. c. water. The results are shown graphically in figure 90. While several short periods of sleep produced rather marked variations in all three factors, the general result of the ingestion of this amount of dextrose was to increase the quotient to approximately 0.90 at about the third half hour after ingestion, with a subsequent fall in 2 hours to nearly the preliminary level of 0.79. There was no change in oxygen absorption other than that due to activity, and no change in pulse-rate which can be ascribed to the dextrose solution.

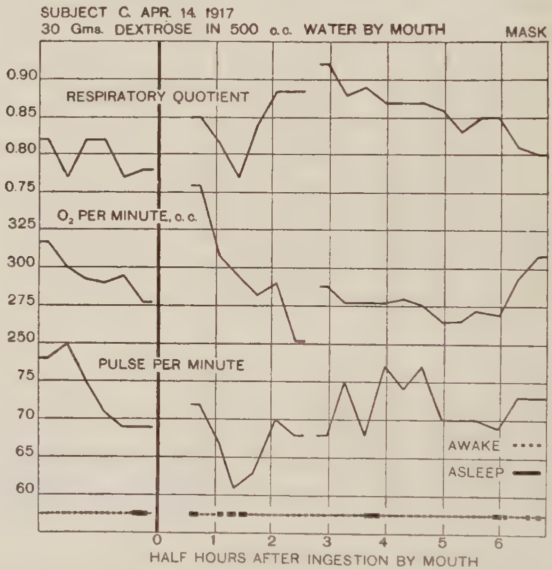


Fig. 90.—Respiratory quotient, oxygen absorption, and pulse-rate of subject C, April 14, 1917, before and after oral ingestion of 30 grams of dextrose in 500 c. c. of distilled water. (Mask, with continuous observation.)

*Subject C, April 20, 1917.*—Ingestion by mouth, 30 grams levulose in 500 c. c. water. The results are given in figure 91. There was but one short period of sleep at the end of the second half hour after ingestion. The respiratory quotient changed from an average of 0.81 in the preliminary period to a maximum of 0.98 in less than an hour after ingestion, then gradually fell to nearly the preliminary level in 3 hours after ingestion. The general level of the curve for the oxygen absorption is slightly higher after the levulose than that for the preliminary values, which is also true for the pulse-rate.

While the results of these two experiments are quite in line with those obtained with larger quantities in earlier work, they are somewhat different

from the findings with the rectal injection of the same substances in like quantities (see pp. 150 and 155), for with mouth feeding the greater change in the respiratory quotient was produced with levulose, whereas with rectal feeding the more definite alteration in the same factor was found with dextrose. The relationship between oral and rectal feeding will be discussed more completely in the following section.

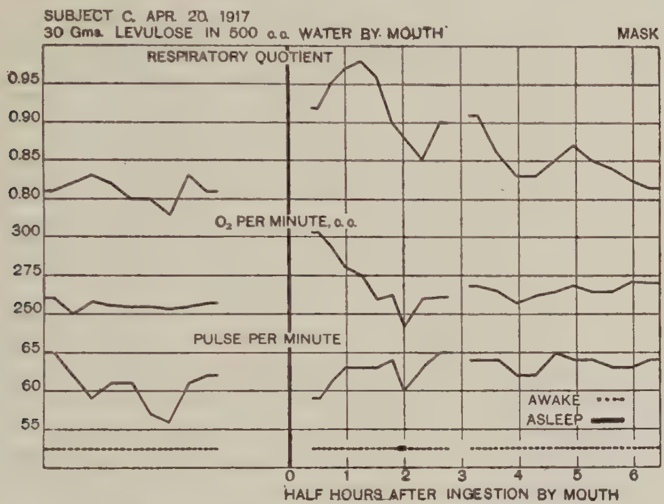


FIG. 91.—Respiratory quotient, oxygen absorption, and pulse-rate of subject C, April 20, 1917, before and after oral ingestion of 30 grams of levulose in 500 c. c. of distilled water. (Mask, with continuous observation.)

# GENERAL DISCUSSION OF RESULTS.

## PRACTICAL CONSIDERATIONS.

The chief purpose of this investigation was the study of the metabolism with rectal injection of various substances. It was therefore not primarily a clinical study, and consequently its value as a clinical contribution is not of chief importance. There are, however, a number of practical points as to the clinical use of rectal feeding which may be considered in the light of the experience which has been obtained in these experiments. The chief objections to giving nutriment by rectum are the discomfort to the patient and the fact that the injections can not be continued very long. It is therefore advisable to consider the subjective impressions of the individuals who underwent these experimental conditions to find if they have practical value in clinical work.

### TEMPERATURE OF MATERIAL INJECTED.

One prominent feature of the reports made by the subjects was the statement that the liquid felt cool, notwithstanding the fact that the solutions when placed in the container were generally at or about body-temperature, i. e., from 37° to 40° C.; in one case the temperature of the solution was 45° C. The container was a glass leveling-bulb of sufficient size to hold a liter or

more of the enema. From the container the solution usually ran down through a rubber tube into a catheter and thence into the rectum of the subject; the solution thus had an opportunity to cool before reaching the man's body.

The drop method described by Murphy[1] necessitates the use of an electric warming-tube at or near the entrance of the catheter. Various methods have been suggested for keeping the solution warm, such as hot sand-bags, hot-water bottles, and similar devices. Kemp[2] discusses the temperature of enemas, the highest considered being 120° F. In this connection he publishes a table showing that when the temperature of the water in the container is 193° F., the temperature of the liquid as it finally reaches the rectum is only 115° F., the difference in temperatures being dependent upon the number of drops entering the bulb per minute, the length of the rubber tubing, and the environmental temperature. Water with a temperature in the container of 115° F. will enter the rectum at the same temperature when flowing at the rate of 200 drops per minute. This rate of flow is somewhat faster than that ordinarily used in the Nutrition Laboratory with the drop method, the rate generally employed here being about 1 drop per second, that is, 60 drops per minute.

On the general principle that physical and chemical reactions proceed faster at the higher temperatures, it is desirable to have the solution as warm as possible without danger of injuring the lining of the colon; at least, the solutions should not be cold, as this is liable to cause a high tonic condition, with consequent peristalsis. Warmth tends to produce relaxation, which is desirable in rectal feeding, as the one thing to avoid is a tonic condition. Olschanetzky[3] studied the time of appearance in the urine and saliva of the reaction for iodine after rectal injection of potassium iodide. He found that the warmer the solution was when injected, the sooner the reaction took place. He also studied the time of disappearance of the reaction and found with lithium carbonate that it was from 44 to 48 hours when the solution was injected cold. When injected at 25° C., it disappeared in 44 hours, at 35° C. in 24 hours, and at 40° and 45° C. in 20 hours. Thus, the time of appearance and the rate of elimination of these substances were influenced by the temperature of the solution when injected.

## Rate of Flow.

In the experiments in this research, the rate of injection varied from 265 c. c. in 1 minute to 1,000 c. c. in several hours. Other things being equal, the slower rates of flow are the more desirable, as the possibility of sensation by the subject is thus avoided or diminished. If the solution is introduced rapidly at first, the amount of sensation felt by the subject is out of proportion to the amount of solution introduced. The threshold for sensation, that is, the amount introduced per minute sufficient for the subject to be conscious of it, may at first be low. After the flow has started, the rate may be increased, with less probability that the subject will realize the change. Apparently, this sensation as to rate of flow varied at times, because in a number of cases the subjects reported that they thought the solution was

[1] Murphy: Jour. Am. Med. Assoc., 1909, 52, p. 1248.
[2] Kemp: Handbook of Medical Sciences, 1914, 4, p. 40.
[3] Olschanetzky: Deutsch. Arch. f. klin. Med., 1890, 48, p. 619.

flowing very rapidly when, as a matter of fact, it was being introduced at a rate of not more than one drop per second.

The consciousness of the passage of the liquid into the rectum is also dependent to a certain extent upon the temperature of the solution. When the liquid is cold, its passage is felt more quickly than when it is introduced at or about body-temperature, as in the latter case the only sensation would be the mechanical effect of its introduction rather than the double sensation of the rate of flow and the difference between the temperature of the body and that of the solution. We have found that the drop method is most satisfactory when volumes larger than 250 c. c. are to be introduced. The drop method has but one disadvantage, namely, that previously stated, that the solutions may cool considerably between the time they are prepared and the time that they reach the colon. One advantage of the drop method is that there is less liability of a large and sudden accumulation in volume, with consequent increase in pressure; also, when concentrated solutions are used with this method, there is less danger of peristalsis and cramps.

A method for avoiding difficulty due to sudden changes in volume and one which requires very little attention to the introduction of the liquid has been proposed by McClanahan.[1] During medical attendance in the Virgin Islands he did not have adequate assistance, and so arranged that the container and tubing should be set at a level at or about the height at which the tube entered the rectum. He claims that in this way there can be no pressure due to accumulation, and if peristalsis begins the solution goes back into the container. The whole matter of feeding is automatically taken care of by placing the container but slightly above the level of the body.

### Volume of Injection.

Most of the recommendations for rectal feeding suggest a volume for the injection of 250 to 500 c. c., and these two volumes represent those which are actually practical. Other things being equal, a volume of 250 c. c. is preferable because there is less danger of accumulation and pressure, with peristalsis as a result. In a number of cases in this research, 1,000 c. c. were given in a short period of time, but this caused cramps and increased pressure which was greater than desirable. It is better to give small volumes intermittently rather than to attempt the injection of a considerable volume in a short period of time.

### Maximum Time of Retention.

In the observations here made there is no attempt to determine the ultimate time so far as retention was concerned. It has been brought out in the literature and also in our own experiments that apparently the greater part of the absorption takes place in the first 2 hours; consequently, when it is desired to inject as much as possible there will be but little gained by waiting longer than 2 hours before a second injection is given, as the additional absorption which may take place from a 5 or 10 per cent solution is not great enough to warrant extending the period of absorption. Whether or not the absorbed liquid should be removed before a second injection is given is not determined by these studies. In fact, it might be possible to give a second injection in an even shorter period of time than 2 hours. We have no data

[1] McClanahan: Jour. Am. Med. Assoc., 1921, 76, p. 174.

on this particular point, but it is a feature of rectal injection which must be considered when as much material as possible must be introduced in a short space of time.

### Position of Subject During Injection.

In the majority of the experiments, the injection was given with the subject lying on his back, although it is generally recommended that the subject should lie on his right side, in the so-called "knee-chest" position. According to Cannon,[1] the matter of gravity plays but little rôle in the question of digestion and absorption in the alimentary tract. The suggestion that with the subject lying on the right side, the solution will reach the transverse colon and pass into the ascending colon has therefore but little practical value. Case[2] says that the "knee-chest position for enemas is quite unnecessary, for unless there is some growth or obstruction, the colon fills easily when the patient lies supine." In several of the experiments in this research, the subject was in the sitting position, but this attitude is apparently not so favorable for rectal feeding as that with the subject lying on his back.

That the supine position is most favorable is also shown by the fact that the pressure in the tubing was much less when the subject was lying on his back than when he was sitting. Indeed, it would seem desirable to employ a pressure indicator of some kind in rectal feeding. With one subject, 1,000 c. c. were given in a little over 2 hours; cramps and intense peristalsis developed and the back-pressure, i. e., the height to which the solution rose in the tubing when no feeding was taking place, was 34 cm., the column of the solution rising and falling with the respiration. In many cases when the subject was lying on his back, the pressure was never more than 10 cm., even though the solution was fed rapidly, and frequently there was entire absence of pressure in the tubing. Joltrain, Bauflè, and Coope[3] describe an instrument (a telenteromanometer) for measuring the colonic pressure, but this was devised after the present research had been made.

### Use of Sodium Chloride.

It is customary with any solution which is to be retained and absorbed to include sodium chloride in a concentration of 0.6 per cent, that is, a solution isotonic with the blood. Such addition does not appear to be necessary, for unless the body needs sodium chloride it does not seem desirable to increase the amount to be absorbed, particularly as with material introduced by mouth no effort is made to use isotonic solutions or to add sodium chloride in such quantity as to make the solution isotonic with the blood. Logically, to secure a proper solution for rectal injection, one should likewise add all of the other constituents which are inorganic and isotonic with the blood. When the body has been actually dehydrated it may be desirable to add distilled water rather than to give a solution containing inorganic constituents.

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[1] Cannon: The mechanical factors of digestion, New York, 1911, p. 48.
[2] Case: Medical Clinics of Chicago, January, 1917, 2, p. 830.
[3] Joltrain, Bauflè, and Coope: Bull. de la Soc. Méd. des Hôpitaux, Paris, 1919, 43, p. 211.

### Addition of Opium.

In a number of the experiments, that is those with the sugars, 5 to 10 drops of tincture of opium were added. This procedure is almost universally recommended for the purpose of preventing peristalsis or pain. There is no evidence in the experiments of this research that the addition of tincture of opium was either beneficial or disadvantageous. Leubuscher [1] studied the effect of different substances upon intestinal absorption. He injected in similar loops of intestine solutions of potassium iodide or of dextrose with and without drugs. The addition of morphine or opium lowered the absorption about one-fourth or one-third. The addition of 0.5 to 2.0 per cent of alcohol caused an increase with potassium-iodide solution, while 4 to 10 per cent depressed the absorption. The 0.5 to 1.0 per cent of alcohol caused an increase in the absorption of dextrose, while with 2 per cent the absorption usually was less than from water solution alone.

While the use of opium is commonly recommended, it would seem more logical to give attention to eliminating conditions which induce peristalsis, such as cold solutions, large volumes, and anxiety on the part of the subject, rather than to add an inhibiting drug which, though possibly a preventive of peristalsis, would at the same time lower the rate of absorption.

### Removal of Unabsorbed Material.

The chief difficulty in determining the absorption in rectal feeding is the fact that the cleansing enema, or wash-out, taken at the end of the observation in rectal feeding experiments, does not remove all of the substance unabsorbed. Very few studies have been made to determine whether a second wash-out removes additional material. Schoenborn [2] used 500 c. c. of water for his first wash-out and, in order to prove that this removed all the unabsorbed sugar, he gave a second and reports that he never found sugar in the material from the second wash-out. Bergmark [3] usually had first a defecation, and then two wash-outs of 250 c. c. each, and tested the material obtained for sugar. He reported that the second wash-out always gave negative results.

In the experimental work here recorded, it is shown that, in general, there was some unabsorbed material not washed out after the first enema was given at the end of the observation. On the other hand, there were several experiments in which no material remained in the rectum, or in which the quantity obtained in the second wash-out was so small as to be of no significance. There is great need for a substance that can be introduced that will not be absorbed, but whose quantity can be determined accurately by chemical or physical means, so that we may find (1) whether a first wash-out removes all of the unabsorbed material; (2) whether the size of the wash-out makes any difference; and (3) whether any of the material passes by the ileocecal valve.

That the solutions actually passed well up into the colon is confirmed by the fact that the subjects reported feeling its passage across the abdomen

[1] Leubuscher: Verhandl. des Cong. f. inn. Med., 1890, p. 436.
[2] Schoenborn: Zur Frage der Resorption von Kohlehydraten im menschlichen Rectum. Diss., Würzburg, 1897.
[3] Bergmark: Skand. Arch. f. Physiol., 1915, 32, p. 355.

and down the right side, and Cannon and Case have each shown that solutions have passed both into the colon and into the cecum. The passage of material through the ileocecal valve is more of theoretical than of practical importance. If it is desired to administer materials rectally, it is of little significance whether the substance passes into the body through the ileocecal valve or whether it is absorbed in the colon. But when one is studying the effect of introducing substances rectally with special reference to absorption from the colon and its further paths into the body, it is of special importance that one should know whether it does or does not pass the ileocecal valve. In a number of investigations this difficulty has been overcome by using various mechanical contrivances to prevent its passage through the valve. In one instance, a heavy weight or pressure was put upon the right side to prevent material from passing by. In several studies (see pp. 3 and 7), a distensible balloon or tampon was inserted far enough into the rectum to close off a short length of the lower part of the intestine and make it available for the absorption of injected solutions. With animals, operations have been performed in which the ileocecal valve has actually been tied off, so as to make sure that no material passed by it.

Studies have likewise been made by means of the Roentgen ray, particularly by Case,[1] from which it has been found that the passage of the material through the ileocecal valve is somewhat dependent upon the volume and also upon the pressure used in forcing it into the colon. Substances such as lycopodium powder have also been introduced with the idea of finding whether they traveled up the alimentary tract, and they have been found in the stomach.

The volume of wash-out after injection should not be less than 500 c. c. Judging from experience in these investigations, three of these will remove practically all of the unabsorbed material which can be reached in this way.

For the cleansing enemas before the feeding is begun, it is desirable to give them in such number and of such size that the colon will be free from fecal and unabsorbed material before the injection. At first this was not so carefully controlled in our experimental work, but later, the subjects followed faithfully the instructions to use a liter of warm water while they were in a sitting position and to repeat this procedure until the last wash-out showed practically no material brought away, that is, the rejected liquid was practically clear. In spite of this care, however, there were instances in which the final wash-out showed that fecal material had apparently traveled down into the large intestine and was removed when the final wash-out was given.

## SUBJECTIVE IMPRESSIONS REGARDING THE VARIOUS SOLUTIONS.

### Sodium-Chloride Solutions.

According to the subjective impressions of the subjects, the solution of sodium chloride did not cause peristalsis or desire to defecate during the time of retention. In two instances, subject B on October 21, and subject A on March 14, the men reported after the experiment that in one case there was diarrhea and in the other there was a tendency for the bowels to be irregular or more frequent in movement, with a desire to defecate. The subjects in

[1] Case: Proc. XVII International Cong. of Medicine, London, 1914, Sect. Radiology, p. 1.

many instances could not tell when the solution was injected, this usually being due to the fact that they were asleep at the time.

### Alcohol Solutions.

The subjects had various ideas as to the material contained in the solutions. One man reported tasting alcohol about 20 minutes after an alcohol solution had been injected. It was suggested to him that he report again when he thought alcohol was given and in one experiment when a solution of sodium chloride was given to him, he again said he tasted alcohol at about the same time as before. Afterwards he was doubtful as to whether the material given was alcohol and could only say that it had a sweetish taste that lasted a long time.

*5 per cent alcohol solution.*— In most of the cases in which the subjects received a 5 per cent alcohol solution, even if it were given when they were asleep, on waking they thought, and in some cases were certain, that the solution contained alcohol. They could not always give their reasons for this belief, but one subject reported that after alcohol there was likely to be some gas in the colon which was removed in the final wash-out.

*7.5 per cent alcohol solution.*— Subject D reported tasting alcohol, but, as previously mentioned, he also reported tasting it when the solution of sodium chloride was given. Subject A reported flushing, perspiration of the feet, and drowsiness with a 7.5 per cent alcohol solution. Subject A on February 3–4, 1917, said on waking up some time after the injection that he felt intoxicated. The same subject, however, a month later reported that he thought the injection was a sodium-chloride or sugar solution, although he was still getting the same quantity of alcohol, namely, 500 c. c. of a 7.5 per cent alcohol solution.

*10 per cent alcohol solution.*—Subjects A and C reported with a 10 per cent alcohol solution that they believed that alcohol had been given them, as they felt warm and intoxicated.

*Maximum alcohol effect.*—The most marked effect of giving alcohol was with subject C on April 18, who received 810 c. c. of a 7.5 per cent alcohol solution over a duration of several hours. He left the laboratory in the latter part of the afternoon, went immediately to the medical school near by, smoked, and remained a half hour. He found that his feet and legs did not seem to obey him, and while his mind was clear it was inclined to be sluggish. He then went into the city but was very pale and nauseated. He was somewhat relieved by taking a cup of coffee, but had no appetite, with a positive distaste for broth. He ate nothing until 11 p. m. and then had a light lunch. During the night he was sleepless and read until $1^h 30^m$ a. m., but felt no after effects the next morning. The quantity he received (60 grams) was much larger that in any of the other experiments.

### Sugar Solutions.

*Dextrose.*—Of 10 experiments with dextrose, there were 2 in which the subjects reported cramps, and difficulty of retention. Subject A, who received 1,000 c. c. of a solution containing 60 grams of dextrose on April 28, 1916, reported periodical cramps, but these disappeared when the final enema was taken. Subject A also reported cramps on February 22, 1917, and found

it difficult to remain quiet. All of the other experiments were without particular sensations or discomfort.

*Levulose.*—Subject C, in experiments on January 25 and February 15, reported cramps and peristalsis. Subject D on January 28 had still more difficulty. This, however, was due to the conditions of the experiment, as he was in the sitting position and the large volume of the solution (1,000 c. c.) was introduced somewhat rapidly. Subject A on January 18 had cramps, and on January 15 reported discomfort and a strong desire to defecate.

### General Summary of Impressions.

The subjective impressions of the men used for this research indicate that the solution of sodium chloride caused no particular difficulty; alcohol appeared to produce drowsiness, flushing, and unsteadiness in a number of cases; dextrose had no effect in most of the experiments; and levulose caused more distress and was more difficult to retain than any of the other materials used in this investigation.

## THEORETICAL CONSIDERATIONS.

### Utilization of Alcohol in Rectal Feeding.

The foregoing sections give the data, with summaries, which were obtained in the study of the rectal feeding of alcohol and of solutions of sodium chloride, levulose, and dextrose. The results of these injections have been studied from the standpoints of absorption of the material introduced, the effect upon flow of urine, the elimination of alcohol in the urine, the periodic variation of the alcohol in the urine, the effect upon the volume of urine and some constituents, and the influence upon the pulse-rate, the respiratory quotient, and the oxygen absorption. It is the purpose here to discuss the evidence which these results give of the utilization of the different materials which were injected into the rectum. As most of the study is concerned with the rectal injection of alcohol, its utilization, as indicated by the results obtained in the various phases of the study, will be discussed first.

#### ABSORPTION OF ALCOHOL AS AN INDICATION OF UTILIZATION.

It is evident that a substance will not be utilized in the body if it is not absorbed. On the contrary, the fact that it is absorbed does not indicate utilization, even though it is of first importance that we know whether or not the material is actually absorbed. When alcohol is given by mouth it is evidently utilized, since its excretion in the urine, breath, and through the skin constitutes a very small proportion (under 5 per cent) of the total amount ingested. The absorption experiments with rectal injection furnish evidence that the material injected was retained in the body. (See p. 27.) In these experiments a second wash-out was given in a number of instances to obtain proof as to whether the first wash-out had removed all of the unabsorbed material. It was often found, when these two wash-outs were used, that either no alcohol was found in the first, so that it was unnecessary to analyze the material from the second, or else that when some unabsorbed alcohol was found with the first wash-out, none was secured from the second.

In two absorption experiments with a 5 per cent alcohol solution, namely, those with A on May 16 and with C on May 13, there was a slight amount in

the second wash-out, so that it is not certain that all of the unabsorbed alcohol was completely removed. In the six experiments with a 7.5 per cent alcohol solution, there was only one experiment in which a second wash out showed alcohol in the material obtained. In all of the experiments with the 10 per cent alcohol solution there was a second wash-out which was without result in every case, showing that the first wash-out removed completely the alcohol which was unabsorbed, that is, that which might remain in the rectum and colon. The evidence from these absorption studies, therefore, is that the alcohol when injected rectally was retained by the body and entered into its tissues. In fact, the absorption was almost complete, being usually over 98 per cent.

### EXCRETION OF ALCOHOL IN URINE AS A MEASURE OF UTILIZATION.

In this research there were two groups of determinations of the amount of alcohol excreted in the urine, one series in which the alcohol was determined in urine collected over a long period of time, and a second series in which the urine was collected in short periods of time and the alcohol content of the individual samples determined. In all but two experiments in which alcohol was given by rectum, alcohol was found in the urine. This, in itself, is not an indication of the utilization of alcohol, but rather evidence to the contrary. It is, however, evidence of the fact that alcohol has entered into the body in such a way that it is eliminated through the kidneys, showing that the alcohol has traveled from the point of entrance and been distributed throughout the body. One might take the ground that the passage of alcohol into the urine was a matter of simple diffusion from the rectum directly through the bladder-wall and thus into the urine. Undoubtedly there is direct diffusion, as animal tissue, even if not active, will absorb alcohol. This fact has been demonstrated in another alcohol study [1] in which the effects of inhalation of alcohol by fowl and its distribution throughout the body was observed. In connection with these observations, dead fowls were placed in an atmosphere of alcoholic vapor and the amount of alcohol in the tissues determined after a certain period of time. It was found that the tissues had absorbed an appreciable amount of alcohol, thus indicating that simple diffusion does play a certain part in distribution throughout the tissues when alcohol is introduced into the body. To assume that diffusion was the sole cause for the elimination of alcohol in the urine would involve the assumption that no alcohol reached the blood, and therefore that no alcohol was eliminated by kidney secretion. This assumption is highly improbable, as on two or three occasions the odor of alcohol was clearly apparent to the observer in the breath of the subject, and there were subjective impressions such as sometimes occur after the taking of alcohol, i. e., flushing of the skin, perspiration, and a slight sense of intoxication. (See p. 165.)

The experiments with long periods of collection do not afford any particular evidence as to the rate of the utilization of alcohol. However, they do demonstrate in the main that the amount of alcohol eliminated is greater when the concentration of alcohol in the solution injected is higher and when the amount injected is larger, thus indicating that a larger amount of alcohol is absorbed or that the absorption takes place so rapidly that the amount in the urine reaches a higher percentage.

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[1] Carpenter and Babcock: Am. Journ. Physiol., 1919, 49, p. 128.

The striking fact about the matter of utilization which the long periods of urine collection show is that when 37.5 grams of alcohol were given in 500 c. c. of a 7.5 per cent solution, and the subject slept practically the entire night, the concentration of alcohol in the urine was considerably higher (see p. 43) than in all the other cases. While the amount injected was somewhat greater than the amount usually given in the other experiments, nevertheless, the concentration was so high in these night experiments that it leads one to think that sleep may have had an influence upon the utilization of alcohol and that there may not be so complete or so rapid a utilization of alcohol when the individual is asleep immediately after or during the taking of alcohol as when the subject is active. This seems the more probable, as the experiments with fowl previously referred to give evidence that activity during the time of inhalation decreases the final concentration of alcohol in the body.[1] The lower alcohol concentration in the hens which were most active would seem to point to the probability of alcohol serving as a source of energy for muscular work.

In contrast to the urine studies with long periods of collection, the experiments in which the urine was collected in short periods give concrete evidence of the utilization of alcohol with both rectal and oral administration. The results bring out clearly the fact that there is a peak in the concentration of alcohol, when absorption and utilization balance one another. Within the first two hours after the alcohol is given, its absorption is faster than its utilization, with, in consequence, increasing concentration in the urine. One must not conclude that this rise in the curve indicates the amount of absorption and from the concentrations shown attempt to compute total absorption values, for the utilization may begin immediately after ingestion; otherwise the peak of the concentration would be very much higher than that shown in most of the experiments.

It is of interest to know the relationship between the alcohol in the urine and that in the body and between the changes in the alcohol contents of both urine and body. Widmark,[2] Nicloux,[3] and Chabanier and Loring[4] made a number of experiments in which they came to the conclusion that the alcohol in the urine and the alcohol in the blood were identical at any given point of time. Widmark conducted experiments on himself in which he took alcohol, catheterized himself, then collected the urine in very short periods, and also took samples of blood at various intervals. He found that the amounts of alcohol in the urine and blood were almost identical. Chabanier and Loring carried out experiments on dogs and obtained like results. They both came to the conclusion that the distribution of alcohol between blood and urine was a matter of simple diffusion, and therefore that blood and urine were identical in concentration of alcohol.

Miles,[5] in this Laboratory, has studied the subject in great detail, using a large number of subjects, collecting the urine in short periods (30 minutes each), and taking blood samples at intervals. He used 27.5 grams of alcohol in water, grape-juice, and alcohol-free beer, in concentrations of 2.75 and

[1] Carpenter and Babcock: Am. Journ. Physiol., 1919, 49, p. 128.
[2] Widmark: Skand. Arch. f. Physiol., 1916, 33, p. 85.
[3] Nicloux: Recherches expérimentales sur l'élimination de l'alcool dans l'organisme. Détermination d'un "alcoolisme congénital". Thesis, Paris, 1900, p. 7.
[4] Chabanier and Loring: Compt. rend. Soc. de Biol., 1916, 79, p. 8.
[5] Miles: Journ. Pharm. and Exp. Therapeutics, 1922, 20, p. 265.

27.5 per cent. In practically all cases he found that in the first 45 minutes the blood-alcohol was higher than that in the urine, but at the end of the first hour the alcohol concentration in the urine was invariably higher than that in the blood, in many cases 50 per cent higher. The blood was collected from the arm; consequently it was venous blood, and Miles calls attention to the fact that the difference between the alcohol-contents of the venous and the arterial blood might be sufficient to account for the difference between the blood-alcohol and the urine-alcohol.

Gréhant[1] points out that the concentration of alcohol in the blood after a definite quantity has been taken would be the same as that which would be expected if it were evenly distributed throughout the body. For example, when a dog received 5 c. c. per kilogram of body-weight, the alcohol content of the blood was 0.5 per cent.

Mellanby[2] found with a dog weighing 13.5 kg. that the amount of alcohol in the blood was somewhat higher than would be expected according to Gréhant's experiments, and says that the Gréhant results are a matter of coincidence. He believes that there is not enough basis to warrant the general assumption made by Gréhant. Mellanby brings out the idea that the concentration in the blood of the dog is inversely proportional to the body-weight; that is, a dog with a weight of 11.75 kg. had a concentration of 92 cubic millimeters per 100 grams of blood, whereas a dog weighing 13.5 kg. had a concentration of 84 cubic millimeters. The ratio of the body-weights was as 1 : 0.87, while the inverse ratio of the alcohol concentration was 1 : 0.91.

The two subjects with whom most of the experimental work here reported was done, namely, subject A and subject C, weighed 54 kg. and 69.7 kg., respectively. If 25 grams of alcohol were distributed throughout the body, there would be an average concentration of 0.46 mg. per gram of body-weight with subject A, and 0.36 mg. with subject C. These values are both higher than most of the values in the urine obtained with these subjects, although subject C, on May 6, with 250 c. c. of a 10 per cent alcohol solution had a concentration of 0.36 mg. per cubic centimeter of urine, which is about the same value as that calculated from the total body-weight. (See table 12 and fig. 3, pp. 46 and 51.)

If, however, it is assumed that the alcohol is distributed throughout the blood only, and that the blood is one-twentieth of the body-weight, we may use as the basis of our calculations 2.7 kg. as the weight of A's blood and 3.5 kg. as the weight of C's blood. With 25 grams of alcohol distributed through the blood, the concentration would be 9.3 mg. per gram of blood for A and 7.1 mg. per gram of blood for C.

If we assume that 60 per cent of the body is water, we may make similar calculations of the distribution of alcohol throughout the water in the bodies of these subjects. The water contained in A's body would weigh 32.4 kg., and in C's 41.8 kg. With 25 grams of alcohol, the concentration with subject A would be 0.77 mg. per gram of water and with C, 0.60 mg. per gram of water.

These calculations of concentration of alcohol in the body all give higher values than the highest found in the analysis of urine. Miles has shown that the urine-alcohol was higher than that in the venous blood, so that probably

[1] Gréhant: Compt. rend. Soc. de Biol., 1881, 1896, 1899.
[2] Mellanby: Med. Research Com., Sp. Rept. Ser. No. 31, 1919.

there is no tissue whose alcohol concentration is higher than the alcohol in either blood or urine. The fact that at the end of 2 hours the urine rarely, if ever, had an alcohol concentration even approximating any of the calculated concentrations in the preceding paragraphs is of significance, because it points towards a rapid utilization of alcohol in the first 2 hours. The objection to this idea would be that possibly not all of the alcohol had been absorbed.

Unfortunately, there are very few experiments in the series here reported which give an idea as to the actual rapidity with which alcohol is absorbed. Most of the absorption experiments indicate nearly complete absorption; consequently, whether the absorption required all the time the enema was retained or whether it took less time can not be determined from the data. On December 20 there was an experiment with subject C (see table 2, p. 27) in which 25 grams of alcohol were given in a 5 per cent solution and retained only 2 hours and 3 minutes. The analysis of the material from the wash-out indicated an absorption of 80 per cent. In an experiment with the same subject on November 29, 21 grams were retained 2 hours and 45 minutes, with an absorption of 98 per cent. With a 7.5 per cent solution there were two experiments in which the time of retention was short. (See table 3, p. 29.) On April 10 there was an absorption of 98 per cent of 350 c. c. (26.25 grams of alcohol) when the enema was retained 1 hour, and on April 15 there was an absorption of 87 per cent of 500 c. c. (37.5 grams of alcohol) in 1 hour and 4 minutes. With a 10 per cent alcohol solution there was an experiment with subject A on March 24 (see table 4, p. 30) in which the absorption was 100 per cent, with a retention for 2 hours and 30 minutes of 260 c. c. (26 grams). While these results are variable, they all show that the absorption of 5, 7.5, and 10 per cent solutions of alcohol given by rectum is very rapid. As the minimum absorption was 80 per cent in 2 hours, it must be concluded that the cause for the difference between the concentration of alcohol in urine as found and the theoretical calculated values shown in the preceding paragraphs is not due to the slowness of absorption. If these low urine-alcohol values are not due to lack of absorption of the alcohol from the rectal tract, then they must be due to rapid utilization in the first 2 hours.

As pointed out previously, the concentration of alcohol in the body at any given moment is a resultant of the balance between the absorption and utilization. The first collection of urine in most of our experiments showed the highest values of the series for alcohol concentration. In other words, this collection probably was not taken at such a time that the absorption was faster than the utilization. (See pp. 52 and 168.) Also, the majority of the first collections were within the first 2 hours. Consequently, if we can calculate the total amount of alcohol present in the body at the first urine collection and assume that the difference between this amount and the amount injected represents the amount utilized, we can gain information as to the theoretical rate of utilization of alcohol. Also, calculating the total amount present at the subsequent collections will give information as to the theoretical rate of utilization throughout the remainder of the experiment. The problem, then, is to find the relationship between the concentration of alcohol in the body and that in the urine.

In the study upon fowls previously mentioned, the alcohol concentration in the tissues and in the blood was determined at various times, and it is

possible to make a comparison between the concentration of the alcohol in the blood and that in the whole body. While there are variations in this relationship, it is of sufficient constancy so that it may be said that the concentration of alcohol averages throughout the body about two-thirds the concentration in the blood. Consequently, when we know the concentration of alcohol in the blood of fowls, we may then compute the average concentration of alcohol throughout their bodies.

To apply this relationship for fowl to the human body requires an assumption, for such a relationship has not been determined for humans. A comparison of the composition of the fowl's body with that of the human body will, however, give some suggestion as to whether such application may be made. The composition of the whole human body as given by Vierordt [1] is water 67.6 per cent, protein bodies and derivatives 20.1 per cent, fat 2.5 per cent, and salts 9.2 per cent. Bouchard [2] gives different figures, these being water 66 per cent, protein 16 per cent, fat 13 per cent, and ash 5 per cent. The average composition of fowls as purchased [3] is reported as water 47 per cent, protein 14 per cent, fat 12 per cent, and ash less than 1 per cent. The extreme variation for both water and fat contents is given as 15 per cent. The hen is therefore drier than man and, according to Vierordt's figures, is also fatter. Both of these differences would tend to widen the ratio between the concentration in the whole body and that of the blood, as it was found [4] that fat absorbed the smallest amount of alcohol and, in general, the greater the water-content of the tissue, the higher was the concentration of alcohol. On the contrary, the salts in man's body are larger in amount than the ash in the body of the fowl, and while these are not strictly comparable, the difference is of significance.

According to this comparison of body composition, therefore, the ratio found with hens for the relationship between the concentration of alcohol in the blood and its concentration in the whole body, if used for humans, will assume a larger difference between the two than is actually the case. However, notwithstanding the fact that with humans the concentrations of alcohol in the blood and in the whole body would be more nearly similar than with fowl, we may, for purposes of discussion, consider that the concentration of alcohol in the body is two-thirds that in the blood.

The results obtained by Miles in his determinations of the alcohol in the urine and blood of his subjects make the use of the urine-alcohol as a basis for calculating the rate of disappearance of alcohol from the body in the present research somewhat complicated. One must, in consequence of his results, assume that at the end of the first hour the concentration of alcohol in the blood is at least two-thirds that in the urine. It should be noted, however, that the urine and blood curves given by Miles tend to approach one another in the second hour, and their relationship in the third and fourth hours, over which many of our experiments were extended, can not be ascertained at this time. The results of the present research have established the fact that

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[1] Vierordt: Daten u. Tabellen f. Mediziner. Jena, 1906, 3d Aufl., p. 378.

[2] Bouchard: Compt. rend., 1897, 124, p. 844.

[3] Atwater and Bryant: U. S. Dept. Agr., Office Exp. Sta. Bull. No. 28, 1906, p. 44. It would seem as though this analysis must represent only the flesh portion of the fowl and not include the skeleton, because of the low amount of ash. If both groups of data for men and fowl were calculated on an ash-free basis, the argument would be in no way altered.

[4] Carpenter and Babcock: Am. Journ. Physiol., 1919, 49, p. 128.

25 grams of alcohol will disappear from the urine in 5 to 6 hours (see p. 55) and presumably during this time it must also have disappeared from the blood.

Rosemann[1] takes exception to the idea that the disappearance of the alcohol from the urine is an indication of the fact that the alcohol is no longer present in the blood. While the experimental results available at the time of Rosemann's statement, as well as the technique then used, might warrant such a criticism, at the present time the methods for the determination of alcohol are so exact that when no alcohol is found in the urine it can hardly be assumed that there is an appreciable amount of alcohol in the blood. This is borne out by the fact that the results obtained in experiments with fowl previously referred to indicate that, except in the egg, there is no large store of alcohol in any tissue which is materially higher than that in the blood, even though Lenoble and Daniel[2] maintain that the cerebrospinal fluid retains alcohol several days after it has disappeared from the blood.

For the purpose of calculating the rate of utilization of alcohol, we may assume that the concentration of alcohol in the blood is the same as that in the urine, and that the relationship between the concentration of alcohol in the blood and that in the whole body is as 1 to 0.67. (See p. 171.) To illustrate the calculation of the rate of utilization by this method, use may be made of the data obtained in an experiment in which there was a complete disappearance of alcohol from the urine, namely, that with subject A on December 15, 1915. (See table 12, p. 46.) To find the theoretical amount of alcohol present in the body for each urine period, the concentration of alcohol in the urine obtained from each collection is multiplied by 0.67 and the body-weight of the subject (54 kg.). As the urine collected was the amount secreted throughout the whole period and not that at any one moment, we must also assume that the urine value obtained represents the average concentration of alcohol for this length of time, i. e., the amount of alcohol present at the middle of the period. The calculations of the theoretical amounts present in the body for the successive urine periods are given in table 29. They show that for the period ending at $6^h 30^m$ p. m. (1 hour and 12 minutes after the injection began), the alcohol in the whole body averaged 9.8 grams, and for the period ending at 7 p. m. (1 hour and 42 minutes after the beginning of the injection), it averaged 11.6 grams, that is, the alcohol in this period was absorbed more rapidly than it was utilized. Deducting the latter amount from the total amount actually injected (21.5 grams) leaves 9.9 grams of alcohol apparently utilized in 1 hour and 27 minutes, i. e., from the beginning of the injection to the middle of the second period. This, if true, would be an extraordinarily rapid utilization. For the period ending at $7^h 28^m$ p. m. (2 hours and 10 minutes after the injection began), the amount present was 9.8 grams and the total utilization up to this time 11.7 grams as compared with 9.9 grams for the preceding period. Thus, the additional utilization in approximately 30 minutes was but 1.8 grams, indicating a rapid fall in rate of utilization. The utilization in the next four periods would then be 2.5, 2.9, 2.8, and 0.3 grams, respectively. At the end of the fifth hour the alcohol had disappeared.

We may calculate, also, the rate per minute at which the alcohol disap-

[1] Rosemann: Oppenheimer's Handbuch der Biochemie des Menschen und der Thiere. Jena, 1911, 4, p. 422.

[2] Lenoble and Daniel: Bull. de l'Acad. de Med., 1919, 82, p. 160.

peared from the beginning of the injection to the middle of each period. The first period need not be considered, as during this time the alcohol was being absorbed and the urine collected included a certain amount which had been secreted before the injection began. For the period ending at 7 p. m., we use 87 minutes as the basis of calculation to the middle of the period, and have 0.11 gram as the amount utilized per minute. As the duration of each successive period is added, the rate per minute gradually decreases until for the whole time the rate of utilization averages 0.075 gram per minute. This indicates a change in rate as the observations continued.

TABLE 29.—*Calculation of rate of disappearance from the body and theoretical utilization of alcohol.*

| End of period. | Calculation of average alcohol present in the body during period. $(w \times a \times b)$[a] | Alcohol theoretically utilized, as shown by difference between amount injected (21.5 gm.) and amount present in body. | Utilization per minute, calculated to middle of period from time injection began.[b] | | Calculation of utilization per minute in each period. |
|---|---|---|---|---|---|
| | | | Time. | Amount. | |
| | *grams.* | *grams.* | *min.* | *gram.* | *gram.* |
| 6h 30m p. m. | 0.27 × 0.67 × 54 = 9.78 | [11.72] | [c]36 | 0.33 | |
| | | | | | [d]0.110 |
| 7 00 | .32 × .67 × 54 = 11.57 | 9.93 | 87 | .11 | |
| | | | | | .062 |
| 7 28 | .27 × .67 × 54 = 9.78 | 11.72 | 116 | .10 | |
| | | | | | .077 |
| 8 05 | .20 × .67 × 54 = 7.24 | 14.26 | 149 | .096 | |
| | | | | | .071 |
| 8 51 | .12 × .67 × 54 = 4.34 | 17.16 | 190 | .090 | |
| | | | | | .064 |
| 9 33 | .042 × .67 × 54 = 1.52 | 19.98 | 234 | .085 | |
| | | | | | .009 |
| 10 03 | .033 × .67 × 54 = 1.19 | 20.31 | 270 | .075 | |
| | | | | | .079 |
| | .... ... ... 0.00 | 21.50 | [e]285 | .075 | |

[a] $w$ = concentration of alcohol in the urine (mg. per c. c.) in experiment with A on December 15. $a$ = relationship between the concentration of alcohol in the blood and that in the body, the assumption being made that the concentration of alcohol is the same in the blood as in the urine. $b$ = body-weight of subject A (kg.).

[b] The injection was given between 5h 18m and 5h 47m p. m.

[c] To middle of interval between beginning of injection and end of first period.

[d] Assumed from utilization per minute to middle of second period.

[e] Includes 15 minutes, the remainder of the seventh period.

The rate of utilization per minute for the individual periods may also be calculated, basing this calculation, also, upon the lapse of time from the middle of one period to the middle of the succeeding period. We find the utilization rate by this method of statement to be greatest at the beginning of the observations (0.11 gram per minute) and least for the period between 9h 33m p. m. and 10h 03m p. m. Whatever way the calculation is made, the indications are that the rate of utilization is greatest during the first 2½ hours. To disprove this it would be necessary to make one of three changes in the method of calculation: (1) raise the amount present in the body, i. e., the amount unutilized, for the periods ending at 6h 30m p. m., 7 p. m.,

and $7^h$ $28^m$ p. m.; (2) assume that absorption had been incomplete and it was still progressing after $7^h$ $28^m$ p. m.; or (3) assume that there was some tissue in the body whose alcohol-content was much higher than that of the urine, this being still in question. We have evidence that the absorption is not complete at the end of the first period (at $6^h$ $30^m$ p. m.), as the concentration was higher in the urine in the period ending at 7 p. m. Furthermore, the fall in concentration in the period ending at $7^h$ $28^m$ p. m. was not so great as in the two succeeding periods, so that the absorption as indicated by the concentration of alcohol in the urine was probably not complete until between $7^h$ $28^m$ and $8^h$ $05^m$ p. m. This was about $2\frac{1}{2}$ hours after the injection began, and it corresponds very closely to the probable time of complete absorption as shown in the absorption experiments. (See p. 27.)

The amount of alcohol calculated to be present in the body could be raised by assuming a narrower ratio than 1 to 0.67 between the concentration in the urine and that in the whole body. There is some warrant for this, as the percentage of water in the human body is larger than that in the hen's body. However, if the alcohol content is calculated from the water-content of the body, the concentration would be multiplied by 0.60 of the body-weight, instead of by the factor 0.67, which would tend to lower all the values and indicate an even greater utilization of alcohol in the first 2 or 3 hours.

This discussion is based upon certain assumptions which admittedly are difficult to prove. If we begin with the assumption that the concentration of alcohol in the blood is two-thirds as high as the concentration in the urine, it would be necessary to lower materially the figures in the first hour or two of the observations. The majority of Miles's experiments were not extended beyond 2 hours after the solution was taken, and nearly all of the experiments indicate at the end of that time a tendency for the concentrations in blood and urine to approach each other, and also for the higher concentrations to be nearer together. If we assume for the first three periods a difference between the concentrations of alcohol in the blood and urine, the alcohol utilized in the first 2 hours would be much greater than that shown in table 29. The utilization would also be greatest when the greatest fall occurred, which seems reasonable according to the curves obtained. In fact, the question may be raised as to whether the rate of utilization of alcohol does not follow more or less the mass law, that is, the rate is proportional to the amount present. This would indicate a rapid utilization at first, with a gradually declining rate of utilization. Some of the curves indicate this change in rate, while others show a fall too steady to be a mass-law effect.

One fact must be accepted, namely, that in about 5 hours the 21.5 grams of alcohol are actually utilized, and this gives an average rate of 0.075 gram per minute or 4.5 grams per hour. At the end of that time no alcohol was found in the urine. By present methods, it is possible to detect 1 mg. of alcohol in 100 c. c. of urine; consequently, if no alcohol appeared in the urine, the alcohol present in the body must be so small that it can not be detected.

The exact peak or highest point in the curve for alcohol in urine can not be obtained either for the time or the concentration, but it must be within the first 2 hours, and the concentration is not materially higher at any time than the highest point observed. While the urine may not have the same alcohol concentration as the blood, its concentration must be dependent upon the concentration in the blood, as it is independent of diuresis or the amount of

urine which is voided. If this is so, the concentration must be determined by the concentration of the liquid which is secreted by the kidneys, and this in turn by the concentration of the blood flowing through the kidneys. There is thus a definite relationship between the concentration of alcohol in the blood and its concentration in the urine.

The results of the studies of the alcohol in urine in short periods indicate that the utilization of alcohol in the first $1\frac{1}{2}$ hours must be extremely high, because any method of calculation which may be used shows that the amount of alcohol left in the body at the end of $1\frac{1}{2}$ to 2 hours is not large, and the utilization of alcohol is practically complete at the end of 5 hours. This would mean that with 25 grams of alcohol there was a utilization on the average of 5 grams of alcohol per hour. The mathematical effect of this upon the respiratory exchange will be considered later.

It may seem that this discussion is of little value, because we are not able to arrive at any definite method of calculating the utilization of alcohol. These theoretical calculations do point out, however, the great utility of studies of absorption and of the concentration in the urine and blood when carried on simultaneously. A given quantity may be introduced rectally and the unabsorbed portion determined, at the end of half-hour periods, for example. This would provide information as to the amount available in the body, and by following the urinary concentration of alcohol the time of disappearance can be determined. By varying the quantity injected and the time of retention, a large amount of information may be obtained regarding the disappearance of alcohol from the body. If, in addition, studies are made with the use of a stomach-tube, an opportunity is given for comparing the utilization according to the method of introduction.

### UTILIZATION OF ALCOHOL IN RECTAL FEEDING AS INDICATED BY THE RESPIRATORY EXCHANGE.

The original plan of these investigations was to determine the respiratory exchange after the rectal injection of alcohol with the idea of finding whether or not the alcohol was utilized and of employing the change in the respiratory quotient as an index of such utilization.

Under ordinary conditions of nutrition, the various functions of the human organism are accompanied by the metabolism of three groups of substances—protein, fat, and carbohydrate. The fats and carbohydrates are considered to be metabolized completely to carbon dioxide and water, while a portion of the protein escapes oxidation and passes into the urine. The composition of carbohydrate is such that in its metabolism the ratio of the volume of carbon dioxide formed to that of the oxygen used is 1.00. The fats contain so small an amount of oxygen that the ratio is less, namely, 0.70. With protein the ratio for the part actually burned is 0.81. These ratios are the well-known respiratory quotients. The nitrogen in the urine eliminated in a given period of time is considered to be a measure of the protein katabolized. Since the carbon dioxide and oxygen involved in the metabolism of 1 gram of protein is known, the amount of carbon dioxide given off and oxygen absorbed in the katabolism of carbohydrate and fat may be calculated by subtracting the amount due to the protein metabolized from the total values obtained for carbon dioxide and oxygen. The apportionment of the katabolism between carbohydrate and fat may then be made by utilizing the quantities of carbon

dioxide produced and oxygen absorbed when carbohydrate and fat are metabolized. By means of simultaneous equations, the oxygen and carbon dioxide may be apportioned between these two, or one may utilize the tables of Zuntz and Schumburg as extended by Williams, Riche, and Lusk.[1] The apportionment of the metabolism among these three substances presents, therefore, no serious complications.

When, however, a fourth substance, such as alcohol, enters into the metabolism to a significant extent, the problem is very much more complicated. The chief question is which one or more of the three groups of substances (protein, fat, or carbohydrate) does alcohol replace? Furthermore, what effect does the replacement have on the respiratory quotient and on the relation of oxygen absorption and carbon-dioxide production to heat production?

Rosemann[2] assumed that alcohol, when metabolized, replaces all three substances in the metabolism in the proportions in which they occurred before the alcohol was ingested; that is to say, if 50 per cent of the total metabolism was replaced by alcohol, then the previous metabolism of protein, fat, and carbohydrate would each be reduced 50 per cent. For calculating the amount of oxygen involved in the metabolism of alcohol, he gives the formula $Oa = O\frac{q - qa}{q - 0.67}$

In this formula $Oa$ represents the oxygen used in burning alcohol, $O$ the total oxygen utilized, $q$ the respiratory quotient before alcohol was given, $qa$ the quotient after the ingestion, and 0.67 the respiratory quotient for alcohol. This calculation involves the assumption that the oxygen utilized is the same before and after the taking of alcohol.

Rosemann has calculated the amount of oxygen used in the metabolism of alcohol for some of the experiments of Geppert.[3] Large quantities of alcohol were taken in these experiments (from 70 to 125 c. c.) and the respiratory quotient before the taking of alcohol varied from 0.83 to 0.90. The respiratory quotient after the ingestion of alcohol varied from 0.72 to 0.79. The values obtained by Rosemann with his formula for calculating the oxygen used for alcohol combustion varied from 44 to 77 per cent of the total, indicating that the proportion of the metabolism due to the alcohol was considerable. The amount of alcohol burned according to this calculation varied from 4.2 grams to 9.6 grams per hour, the lower figure being somewhat like the value which has been estimated for the experiments here reported when the alcohol in the urine was considered.

Higgins[4] used the formula of Rosemann for calculating the amount of alcohol utilized in experiments on man, and came to the conclusion that the fall in the respiratory quotients and the calculated amounts of alcohol consumed are not markedly different for 45 and 30 c. c. of alcohol. He calculated that on the average about 27 per cent of the total oxygen was consumed in burning the alcohol with both 30 c. c. and 45 c. c., the variation being from 7 to 54 per cent. The average amount of alcohol burned per hour was calculated as 3.46 c. c. He states that it would take approximately 8 hours for the

[1] Williams, Riche, and Lusk: Journ. Biol. Chem., 1912, 12, p. 357.
[2] Rosemann: Oppenheimer's Handbuch d. Biochem., 1911, 4, (1), p. 423.
[3] Geppert: Arch. f. exp. Path. u. Pharmakol., 1887, 22, p. 367.
[4] Higgins: Journ. Pharm. and Exp. Therapeutics, 1917, 9, p. 467.

total consumption of 30 c. c. and as much as 12 hours for 45 c. c. of alcohol. Higgins likewise gives a table showing that the greater the initial respiratory quotient is when alcohol is ingested, the greater will be both the fall due to the taking of the alcohol and the percentage of the total oxygen which is used for alcohol metabolism.

Durig and coworkers studied the carbohydrate-sparing action of alcohol,[1] using the Zuntz-Geppert apparatus for determining the respiratory exchange. In some experiments they gave 100 grams of dextrose and 100 grams of levulose and followed the respiratory exchange from period to period for 4 hours. With dextrose alone there was a slow but marked rise in the respiratory quotient, with a change in some cases from approximately 0.85 to over 1.00. When, however, alcohol was given with the dextrose, or 1 hour and 40 minutes afterwards, the rise in the quotient found with dextrose alone did not take place, or the upward movement stopped when the alcohol was given. The same general effect was found when alcohol was given in the levulose experiments. In one experiment portions containing 30 grams of levulose each were given at intervals; in another experiment the same procedure was followed, but 30 c. c. of alcohol were given about 40 minutes after the first portion of sugar had been ingested. In the experiment with levulose alone, the respiratory quotient remained at or near 1.00, but with levulose and alcohol there was an immediate fall in the quotient as soon as the alcohol was given, which continued until the quotient was even lower than before the levulose was ingested. Assuming that the alcohol replaced carbohydrate, the authors calculated 70 mg. of alcohol were burned per minute, or 4.2 grams of alcohol in 1 hour, and that in the first 4 hours, 16.8 grams were utilized of the 24 grams given. The experiments show very clearly that the giving of alcohol with carbohydrate, or after the rise in respiratory quotient has begun, either lowers the quotient or prevents the rise which would normally take place due to the ingestion of carbohydrate. Whether this rise in quotient is due to a combustion of carbohydrate or a change of carbohydrate to fat, the interruption is complete, so that the introduction of alcohol into the organism changes a condition of metabolism in which carbohydrate is the predominating factor.

In order to obtain an idea as to the theoretical effect of the utilization of alcohol and its replacement of other materials in ordinary metabolism, a table has been prepared giving the results of calculations in which, with varying apportionments of protein, fat, and carbohydrate in the initial metabolism, alcohol has been made to replace a certain mathematical proportion of the energy production (1 per cent) of one or more of the other three substances. (See table 32.) These calculations show the effect of such replacement upon the respiratory quotient. The values utilized in this calculation are those for glycogen, human fat, human protein, and ethyl alcohol.[2] (See table 30.)

The method of calculating the respiratory quotient and also the calorific equivalents of oxygen and carbon dioxide is illustrated in table 31. In this sample calculation it has been assumed that the total metabolism was 2,000 calories, the substances metabolized being in the following proportions: protein 15 per cent, carbohydrate 25 per cent, fat 50 per cent, and alcohol 10 per cent. To obtain the heat liberated in the metabolism of each nutrient, the

[1] Tögel, Brezina, and Durig: Biochem. Zeitschr., 1913, 50, p. 296.
[2] Carpenter: Carnegie Inst. Wash. Pub. No. 303A, 1924, p. 124.

value for the total metabolism (2,000 calories) is multiplied by the respective percentages assigned to the four substances. The carbon dioxide produced is next calculated by dividing the calories obtained from each by the calorific equivalent of 1 liter of carbon dioxide, namely, 5.69 calories for protein, 5.06 calories for carbohydrate, 6.72 calories for fat, and 7.28 calories for alcohol. (See table 30.) The results added together give the total volume of carbon dioxide produced in the metabolism, i. e., 327.81 liters. The oxygen used in the combustion is likewise calculated by dividing the calories from each material by the calorific value for 1 liter of oxygen, these values being protein 4.60 calories, carbohydrate 5.06 calories, fat 4.79 calories, and alcohol 4.85 calories. The sum of the results represents the total volume of oxygen used—414.04 liters. The respiratory quotient and the calorific equivalents are then readily calculated.

TABLE 30.—*Amounts of carbon dioxide produced, oxygen used, and heat liberated in the metabolism of human protein, human fat, glycogen, and alcohol. (1 gram).*

| Substances katabolized. | Carbon dioxide. | Oxygen. | Heat. | Calorific equivalent of carbon dioxide per liter $\left(\frac{\text{Cals.}}{CO_2}\right)$ | Calorific equivalent of oxygen per liter $\left(\frac{\text{Cals.}}{O_2}\right)$ |
|---|---|---|---|---|---|
| | *liters.* | *liters.* | *cals.* | *cals.* | *cals.* |
| Human protein.... | 0.7738 | 0.9569 | 4.40 | 5.69 | 4.60 |
| Human fat........ | 1.4204 | 1.9908 | 9.54 | 6.72 | 4.79 |
| Glycogen......... | .8293 | .8293 | 4.20 | 5.06 | 5.06 |
| Alcohol........... | .9729 | 1.4595 | 7.08 | 7.28 | 4.85 |

TABLE 31.—*Illustrative calculation of respiratory quotient and calorific values of oxygen and carbon dioxide with changing proportion of nutrients.*

[Total calories = 2,000. Derived from protein, 15 p. ct.; from carbohydrate, 25 p. ct.; from fat 50 p. ct.; from alcohol, 10 p. ct.]

| Nutrients katabolized. | Heat produced. | Carbon dioxide produced. | Oxygen absorbed. |
|---|---|---|---|
| | *cals.* | *liters.* | *liters.* |
| Protein............ | 15×2,000= 300 | 300÷5.69= 52.72 | 300÷4.60= 65.22 |
| Carbohydrate...... | 25×2,000= 500 | 500÷5.06= 98.81 | 500÷5.06= 98.81 |
| Fat............... | 50×2,000=1,000 | 1,000÷6.72=148.81 | 1,000÷4.79=208.77 |
| Alcohol............ | 10×2,000= 200 | 200÷7.28= 27.47 | 200÷4.85= 41.24 |
| Total........... | 2,000 | 327.81 | 414.04 |

Respiratory quotient = 327.81 ÷ 414.04 = 0.792.
Calorific value of carbon dioxide = 2,000 ÷ 327.81 = 6.101 cals. per liter.
Calorific value of oxygen = 2,000 ÷ 414.04 = 4.830 cals. per liter.

The calculations by this method for variations in replacement by alcohol of the different nutrients in the metabolism are summarized in table 32. In the first column of this table is given the respiratory quotient for the original distribution of the metabolism as indicated in the following three columns. Thus, in the first instance given, with heat produced from the metabolism of

10 per cent of protein, 30 per cent of fat, and 60 per cent of carboyhdrate, the respiratory quotient would be 0.891. The fifth column shows the changed conditions in that alcohol replaces the nutrients named in a certain proportion (1 per cent) of the metabolism. If more than one nutrient is replaced, as in the first case, the apportionment of the substitution is made according to the original distribution. In the last column the changes in the respiratory quotients are given for the new distribution of metabolism, the new quotients being lower than the original quotients as a result of the replacement by alcohol of 1 per cent of the total energy originally supplied by the other nutrients.

TABLE 32.—*Theoretical effect upon the respiratory quotient when alcohol replaces one or more nutrients in 1 per cent of the metabolism.*

| Initial respiratory quotient. | Initial percentage distribution of heat from— | | | Alcohol replaces— | Change in respiratory quotient for 1 p. ct. replacement. |
|---|---|---|---|---|---|
| | Protein. | Fat. | Carbohydrate. | | |
| 0.891 | 10 | 30 | 60 | P. F. C. | −0.00224 |
| .925 | 0 | 25 | 75 | C. F. | − .00259 |
| .853 | 0 | 50 | 50 | C. F. | − .00186 |
| .925 | 0 | 25 | 75 | F. | − .00044 |
| .853 | 0 | 50 | 50 | F. | − .00046 |
| .853 | 0 | 50 | 50 | C. | − .00327 |
| .824 | 15 | 50 | 35 | C. | − .00320 |
| .796 | 15 | 60 | 25 | C. | − .00320 |
| .853 | 15 | 40 | 45 | C. | − .00324 |
| .881 | 15 | 30 | 55 | C. | − .00325 |
| .910 | 15 | 20 | 65 | C. | − .00326 |

Table 32 brings out several points. If carbohydrate alone is replaced by alcohol when the initial combination is either fat and carbohydrate, or protein, fat, and carbohydrate, the lowering of the respiratory quotient due to a 1 per cent replacement by alcohol is about the same (0.00320 to 0.00327), regardless of the initial percentage of energy derivable from carbohydrate. Accordingly, if alcohol replaces carbohydrate alone, the fall in the quotient with a 1 per cent replacement of energy would be the same, regardless of the initial quotient. Now, the experiments of Higgins, as well as many of the experiments in this publication, indicate that the higher the initial respiratory quotient, the greater is the fall due to the ingestion of alcohol. If the view is accepted that alcohol replaces carbohydrate only, these findings would indicate that the replacement is greater with a high proportion of carbohydrate in the total metabolism than when the proportion of carbohydrate is low. The experiments of Tögel, Brezina, and Durig[1] favor this view. They found either that the rise of the respiratory quotient due to dextrose and levulose was entirely suppressed or there was an abrupt lowering as soon as alcohol was given. It is popularly believed that the individual accustomed to the use of alcohol does not care for sweets, but that when he is deprived of alcohol he begins to crave them. Although such evidence is unscientific, it is well to keep this belief in mind in connection with the actual experimental results so far as change in the respiratory quotient due to the ingestion of alcohol is concerned.

[1] Tögel, Brezina, and Durig: Biochem. Zeitschr., 1913, 50, p. 296.

An examination of the changes when alcohol replaces fat alone shows much less effect upon the respiratory quotient than when alcohol replaces carbohydrate. Furthermore, as with carbohydrate alone, the original distribution of energy-producing material does not affect particularly the lowering of the quotient due to replacement of fat by alcohol. When, however, carbohydrate and fat are replaced by alcohol in their original proportions, that is, the ratio of carbohydrate to fat is kept the same, but the amount of energy derived from the two is lowered, it is found that the lower the amount of carbohydrate at the beginning, the less the quotient is lowered in the replacement by alcohol. This is an application in another way of the Rosemann idea, except that protein is not included.

One may calculate from this table the probabilities for change in quotient. The majority of the preliminary respiratory quotients in the alcohol experiments in this research averaged between 0.79 and 0.82. If we take, for example, a fall in the respiratory quotient of 0.05 and assume that the change was entirely due to a replacement of fat, then the percentage of the total energy which would be derived from alcohol in such replacement would be equal to 0.05 divided by 0.00045 (the average change in quotient under these conditions shown in table 32). This would amount to 111 per cent, which is of course impossible, and this calculation therefore eliminates the probability of the replacement of fat alone by alcohol. If carbohydrate only were replaced by alcohol, with a lowering of 0.05 in the respiratory quotient, the percentage of the total metabolism replaced would be 0.05 divided by the average change in quotient shown in table 32 with such replacement (0.00324) which would give a replacement of 15.4 per cent. If carbohydrate and fat were replaced in the proportion in which they were being metabolized, then with a lowering of 0.05 in the respiratory quotient, the percentage replacement would depend upon the previous combination, that is, the greater the amount of carbohydrate present, the greater would be the percentage replacement for each 0.01 change in the respiratory quotient. As previously stated, Higgins[1] found that the higher the initial quotient, the greater was the fall when alcohol was given, and the experiments in this research show the same tendency.

In order to have the same rate of utilization, regardless of the original composition, there would have to be a greater fall with a high respiratory quotient if a combination of fat and carbohydrate were utilized before alcohol was given. However, if it were true that alcohol burned at a uniform rate, regardless of the proportions of other materials, it would differ entirely from the others. It has been definitely shown that the higher the proportion of carbohydrate in the diet, the higher the respiratory quotient in a basal condition is, and it is likewise well known that the metabolism level of protein is governed by the protein intake. It therefore does not seem logical to conclude that alcohol is utilized at the same rate, independent of the quantity taken in and independent of the proportions of the three nutrients being metabolized before its introduction. It seems more logical to conclude that alcohol replaces carbohydrate in preference to the other two nutrients, fat and protein.

The question as to whether alcohol replaces protein or spares it is much debated. Rosemann[2] summarizes the findings on this problem up to the

[1] Higgins: Journ. Pharm. and Exp. Therapeutics, 1917, 9, p. 467.
[2] Rosemann: Oppenheimer's Handbuch d. Biochem., 1911, 4, (1), p. 434.

time of his publication, and the evidence is conflicting as to whether the utilization of protein is actually diminished or increased by alcohol. In our experiments the giving of alcohol did not, apparently, cause a marked decrease of nitrogen in the urine or an increase in spite of the marked increase in the volume of urine which would give ideal conditions for washing out nitrogenous end products of protein metabolism. The decrease was not so apparent as with other substances, particularly levulose. It is therefore questionable whether in the calculations it should be assumed that the protein metabolism is reduced by alcohol. Experiments are needed in which both the nitrogen output and the sulphur output are determined in short periods after the ingestion of alcohol. In our calculations it will be assumed that the course of the protein metabolism is unchanged by the ingestion of alcohol. In fact, it would be impracticable to calculate the change in the protein metabolism, as the urine was not collected immediately before and immediately after the alcohol was given.

It is difficult to choose between the two theories (1) whether alcohol replaces carbohydrate only or (2) whether it replaces both fat and carbohydrate. Comparison experiments are needed in which the initial levels of the metabolism vary as indicated by the respiratory quotient and in which after the ingestion of alcohol the concentration of alcohol in the blood and urine is followed periodically until the alcohol disappears. If alcohol replaces carbohydrate only, then when the combustion is essentially carbohydrate there should be a more rapid utilization of alcohol than when the initial respiratory quotient is low. In experiments of this character it should be remembered that when the respiratory quotient is high, there is a natural tendency for it to fall, so the individual should be in such condition, as shown by repeated tests, that the respiratory quotient will remain at a high level over a period of several hours.

Rosemann's formula assumes that after alcohol ingestion the metabolism of the three groups of materials proceeds in the same proportion to one another as before the taking of alcohol. Higgins, in using the formula, assumed that this applied only to fat and carbohydrate. Such an assumption, however, makes very little difference in the calculation, because the respiratory quotient of protein is between carbohydrate and fat. The highest calculated combustion of alcohol in Higgins's experiments was 6.3 grams per hour, which gives a respiratory exchange due to alcohol of 102 c. c. of carbon dioxide and 152 c. c. of oxygen per minute; this is 54 per cent of the total oxygen used in the period.

The amounts of alcohol theoretically utilized have been calculated and are given in table 33. The experiments selected for the calculation are those in which the fall in the respiratory quotient due to the injection of alcohol was most positive. The calculation has been made in two ways. In the first, the Rosemann formula has been used and the assumption made that the alcohol replaces the nutrients in the proportion in which they were being utilized before the alcohol was taken. In our calculation no account is made of the protein, this being in accord with the custom of the Nutrition Laboratory in the calculation of total metabolism from the respiratory quotient. The neglect of the protein in the calculation does not introduce a considerable error as from the theoretical quotient of protein it can be seen that it is practically an average of the other two quotients, that is, the quotient of protein

is 0.81, while the quotients of fat and carbohydrate are 0.70 and 1.00, respectively. In the calculation by the Rosemann formula, it was also assumed that the oxygen absorption remained unchanged after alcohol ingestion. This is not strictly true, as in a number of cases, particularly in the night experiments with a 7.5 per cent alcohol solution, there was a noticeable increase in the oxygen absorption.

TABLE 33.—*Calculated amounts of alcohol used per hour.*

| Date. | Percentage of alcohol in solution, and subject. | Volume of injection. | Respiratory quotient. Before injection. | Respiratory quotient. After injection. Time of minimum from beginning of injection. | Respiratory quotient. After injection. Average minimum quotient. | Oxygen absorption per minute.[a] | Alcohol used per hour (calculated).[b] | Alcohol used per hr., if carbohydrate alone is replaced (calculated). |
|---|---|---|---|---|---|---|---|---|
| 1915. | *5 p. ct.* | *c. c.* | | *hrs.* | | *c. c.* | *grams.* | *grams.* |
| Oct. 24 | C | 325 | 0.79 | 2 to 2½ | 0.75 | 275 | 3.7 | 1.4 |
| Nov. 18 | A | 400 | .81 | ¾ 1¾ | .78 | 195 | 1.7 | 0.7 |
| Nov. 24 | A | 420 | .86 | 1½ 2 | .78 | 200 | 3.5 | 2.1 |
| Dec. 2 | A | 420 | .88 | 1 3 | .79 | 215 | 3.8 | 2.5 |
| 1916. | | | | | | | | |
| Feb. 18 | D | 520 | .81 | 2 3 | .78 | 235 | 2.0 | 0.9 |
| Apr. 17 | A | 1,020 | .80 | 3½ 5 | .76 | 205 | 2.6 | 1.0 |
| | *7.5 p. ct.* | | | | | | | |
| Feb. 28 | A | 265 | .82 | 2½ 3¼ | .76 | 200 | 3.3 | 1.5 |
| Mar. 3 | D | 265 | .80 | 3¼ 4 | .76 | 235 | 3.0 | 1.2 |
| Apr. 10 | A | 350 | .83 | 3¼ 4¼ | .77 | 200 | 3.1 | 1.5 |
| Apr. 15 | A | 500 | .83 | 2¾ 3½ | .75 | 212 | 4.4 | 2.2 |
| 1917. | | | | | | | | |
| Jan. 20–21 | A | 500 | .81 | 1¼ 2¼ | .76 | 200 | 3.0 | 1.3 |
| Feb. 3– 4 | A | 500 | .87 | 3½ 5½ | .77 | 200 | 4.1 | 2.6 |
| Feb. 15–16 | A | 500 | .87 | 1½ 2½ | .78 | 205 | 3.8 | 2.4 |
| Mar. 23–24 | A | 500 | .83 | 3½ 4 | .76 | 220 | 4.0 | 2.0 |
| 1916. | *10 p. ct.* | | | | | | | |
| Mar. 6 | A | 265 | .81 | 2 2½ | .76 | 225 | 3.3 | 1.4 |
| Mar. 8 | C | 265 | .82 | 2 2½ | .77 | 270 | 3.7 | 1.7 |
| Mar. 10 | D | 265 | .83 | 1½ 2¼ | .76 | 220 | 4.0 | 2.0 |

[a] Oxygen at time of minimum quotient.

[b] Rosemann's formula used.

In the second method of calculation it was assumed that the alcohol replaced carbohydrate alone and the theoretical values in table 32 used. According to this table, when carbohydrate alone is replaced and the respiratory quotient approximates 0.79 to 0.82, the theoretical replacement of 1 per cent of the energy production by alcohol results in lowering the respiratory quotient 0.00320. The details of this second method of calculation were as follows: The total heat-production was calculated by utilizing the oxygen absorption and the calorific value of oxygen at the respiratory quotient before injection. The difference between the average respiratory quotient before injection and the average minimum quotient after injection was then divided by the theoretical value for replacement of 1 per cent of the energy from carbohydrate by alcohol, namely, 0.00320. This gave the percentage of the total metabolism which was replaced by alcohol. Multiplying the heat-production by this percentage gave the heat derived from alcohol. The calories derived from alcohol were then divided by the factor

7.08 (see table 30) and multiplied by 60 to obtain the grams of alcohol utilized per hour when carbohydrate alone was replaced.

The amounts of alcohol theoretically utilized, as calculated by the first method, i. e., with the Rosemann formula, which assumes the replacement of all the nutrients by alcohol, are given in the next to the last column of the table. The amounts vary from 1.7 to 4.4 grams per hour. In general, the amounts utilized per hour with a 5 per cent alcohol solution are slightly lower than those with a 7.5 per cent alcohol solution, but it must be noted that the quantities of alcohol actually injected were, in general, somewhat larger with the 7.5 per cent solution than with the 5 per cent solution. The amounts per hour with the 10 per cent solution are of about the same order as with the 7.5 per cent solution although the quantities of alcohol injected were 26.5 grams as compared with 37.5 grams in the last five experiments with the 7.5 per cent solution. According to these calculations from the respiratory quotient, therefore, the amounts utilized per hour are essentially the same, regardless of the amounts of alcohol injected. This finding corresponds with that given by Higgins.

The highest values for alcohol utilized approach somewhere near the values computed from the disappearance of alcohol in the urine. (See p. 174.) The conclusion was drawn from the urine determinations that 25 grams of alcohol disappeared in about 5 hours. This would correspond to about 5 grams per hour. The maximum figure shown in table 33 is 4.4 grams per hour. At the maximum rate of utilization of 4.4 grams per hour, it would take over 8 hours for the 37.5 grams of alcohol given in this experiment to be completely utilized. In the experiments which were continued through the night there was no indication of a return to the original respiratory quotient, even after 6 hours. Experiments are needed to confirm the general idea that these rates as calculated really represent the rate of utilization. If the experiments had been sufficiently long, they ought to have shown that at the end of 5 to 8 hours there was a tendency for the quotient to return to a level approximately that before injection took place.

The figures in the last column show the theoretical values when the alcohol replaces only carbohydrate. In general, these values are much lower, most of them being less than one-half of those in the column preceding. Accordingly, if one assumes that the alcohol replaces carbohydrate alone, the time of utilization would be much longer than when it is assumed that the alcohol replaces all the nutrients. From this comparison, and considering also the time of the disappearance of alcohol from the urine, it would appear that Rosemann's assumption was correct, namely, that alcohol replaces the nutrients in the proportion in which they were being utilized before alcohol was taken. As pointed out before, alcohol must therefore behave differently from any other material used as food. The investigation on the concentration of alcohol in the bodies of fowls after its inhalation[1] indicates that alcohol may serve as a source of energy for muscular work.

The time of the lowest quotient after alcohol injection is given in the fifth column and varies from 1 to 3½ hours. This is simply the expression of the time when the greatest change took place as compared with the quotient before injection, and should not be confused with the time when the earliest change in the respiratory quotient took place. In some cases it will be seen

[1] Carpenter and Babcock: Amer Jour. Physiol., 1919, 49, p. 128.

that it corresponds very closely to the peak of concentration of alcohol in the urine and in other cases it is somewhat later.

The general conclusion from this theoretical calculation is that not over 5 grams of alcohol are actually utilized per hour, irrespective of the quantity injected, and that this value corresponds fairly closely to the conclusions drawn from the urine analyses.

The maximum theoretical percentage of the total metabolism which can be replaced by alcohol is shown by the following calculation: In the experiment with A on April 15, 1916, the oxygen absorption before injection was 212 c. c. per minute which, with a respiratory quotient of 0.83, gives a heat-production of 61.5 calories per hour. The alcohol theoretically utilized in this experiment is shown in table 33 to be 4.4 grams, which, at 7.08 calories per gram, gives 31.2 calories, or 51 per cent of the total heat-production. This is in good agreement with the values found by Higgins with oral ingestion, who gives 54 per cent as the maximum utilization of oxygen in the combustion of alcohol, which corresponds very closely with the percentage heat-production. It would thus appear that the percentage of the total metabolism replaceable by alcohol is about the same, regardless of whether the alcohol is given by rectum or by mouth.

An anomaly brought out by a comparison of the respiratory exchange with the concentration of alcohol in urine is that, according to the urine values, the highest theoretical utilization of alcohol was observed about $1\frac{1}{2}$ to 2 hours after ingestion, but according to the respiratory exchange it would appear that the highest utilization of alcohol was somewhat later than this, particularly in the night experiments, in which the respiratory quotient continued to fall throughout the night. The urine figures indicate the disappearance of alcohol from the body, but if this were true, then the respiratory quotient would begin to rise to indicate a return to previous conditions, but it does not.

The lack of consistency between the evidence supplied by the respiratory exchange and that of the urine determinations suggests the need of further investigation, particularly if arrangements can be made for simultaneous determinations of the alcohol concentration in the blood and urine and of the respiratory exchange. The experiments of Strassmann[1] indicate that the determination of the amount of alcohol in the expired air would likewise be of value as showing the course of the disappearance of alcohol from the body. Strassmann found that after the taking of from 50 to 60 c. c. of alcohol, an average of 2.06 c. c. of alcohol were eliminated in the expired air in the first hour, 1.49 c. c. in the second hour, with diminishing amounts in the succeeding hours, only 0.6 gram being eliminated in the breath during the fourth hour. These were much larger amounts than were found by Atwater and Benedict[2] with individual doses much smaller and more dilute.

Simultaneous studies of the respiratory exchange and the amount of alcohol in the expired air would be of value in correlating the change in alcohol-content of the body with the respiratory exchange.

As brought out in previous discussion, the experiments on rectal feeding indicate that the proportion of the total metabolism due to the alcohol injected may be as high as 51 per cent. The utilization of alcohol in rectal feeding therefore plays a prominent rôle in the total metabolism.

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[1] Strassmann: Arch. f. Physiol., 1891, 49, p. 315.

[2] Atwater and Benedict: National Acad. Sci., 1902, 8, 6th mem., p. 393, table 122.

## Utilization of Dextrose When Introduced Rectally.

The utilization of dextrose is discussed in much the same manner and from the same standpoint as the utilization of alcohol. The absorption studies show conclusively that it was not possible to recover any considerable amount of dextrose when introduced into the rectum in a 0.6 per cent solution of sodium chloride, if the attempt were made within 3 or 4 hours. Fortunately, in all of the absorption experiments, more than one wash-out was given at the end of the experiment, and the second was of such size that the removal of the unabsorbed material should be fairly complete. This is shown by the fact that in a number of instances the amount of dextrose that was actually present in the second wash-out was 0, while in other cases the amount obtained was a very small percentage of the total amount recovered. The actual amount in the second wash-out ranged from 4.2 grams to 0. A third wash-out was given on two occasions. In one no unabsorbed dextrose was found, and in the other but 0.9 gram of the 30 grams introduced. Apparently, therefore, the absorption from 30 grams was 17.5 to 26.3 grams.

It may be suggested that this disappearance was due to a fermentation which takes place in the colon and rectum. No attempts were made in these studies to determine whether fermentation had any part in the disappearance of the dextrose injected. Studies of such character have been made by previous investigators, however, from which they have concluded that while a small amount of fermentation may actually take place (considered as lactic-acid fermentation by Mutch and Ryffel),[1] the material is actually absorbed. This conclusion is corroborated in some of the studies by observations of the blood-sugar which showed a slight increase, thus supplying evidence that the utilization is fulfilled by actual absorption into the circulation of the dextrose introduced.

The studies upon the composition and amount of the urine show that in a number of cases the volume was increased after the injection of a 500 c. c. solution of dextrose, while in others it was decreased; consequently, there was no general directional effect as to change in volume. The nitrogen in the urine changed on the average $\pm$ 25 per cent, but when averaged with reference to sign, there was a directional change of $-13$ per cent, indicating a slight decrease in nitrogen output. This, however, is hardly significant enough to be considered as proof that the injection of this amount of dextrose caused an actual sparing of the protein metabolism.

The maximum change in the respiratory quotient after the injection of dextrose solution occurred with subject A on February 22, 1917, in an experiment with 30 grams of dextrose in a 520 c. c. solution with the subject inside a respiration chamber. The average of the first 3 or 4 respiratory quotients was about 0.86; the giving of the dextrose raised it to an average in two periods of 0.92 during the sixth and seventh half hours after injection, that is, about 3 to $3\frac{1}{2}$ hours after injection. In the experiment with the same subject on May 4, 1916, there was a change from about 0.82 to 0.87, that is, an increase of 0.05. According to the table of Williams, Riche, and Lusk,[2] a change of this magnitude in the respiratory quotient results in a change of more than 15 per cent in the proportion of energy from carbohydrate.

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[1] Mutch and Ryffel: British Med. Journ., 1913, 1, p. 111. See, also, p. 13 of this monograph.
[2] Williams, Riche, and Lusk: Journ. Biol. Chem., 1912, 12, p. 357.

As was done for the alcohol experiments, a calculation has been made of the utilization of the material injected by comparing the utilization of carbohydrate before and after the ingestion of the dextrose solution. The computations in this case, however, were made from the non-protein respiratory quotients. These were obtained by deducting from the values for carbon dioxide and oxygen the amounts due to protein alone, and the quotient found by dividing the remainder for the carbon dioxide by that for the oxygen was the non-protein respiratory quotient. From the oxygen per minute thus obtained, the non-protein respiratory quotient and the calories per liter of oxygen corresponding to the respiratory quotient,[1] a calculation was made of the heat output due to the katabolism of carbohydrate and fat. The amount due to carbohydrate alone was obtained by employing the table of Williams, Riche, and Lusk.[2] This divided by the heat produced in the oxidation of 1 gram of dextrose, namely, 3.74 calories, gave the amount of carbohydrate as dextrose utilized before injection. Multiplying by 60 gave the amount per hour. The same method was used for calculating the utilization after injection, except that instead of an average, the maximum respiratory quotient was taken, preferably from that portion of the experiment in which there was more than one high respiratory quotient. There were only five experiments which appear suitable for such calculation, and the results of these are given in table 34. Three of the experiments were with subject A and two with subject C. The amounts of carbohydrate utilized per hour before injection were 4.4, 4.6, and 7.8 grams with A and 8.9 and 7.3 grams with C. The values for C are larger for two reasons: one, because his actual metabolism was higher, and the other because the respiratory quotient tended to be higher. After injection the increase was greater with A than with C, the values being 8.4, 8.3, and 11.4 grams for A, with a general increase of about 4 grams, while the values for C were 10.2 and 10.3 grams.

The amounts of dextrose apparently absorbed in these four experiments (see p. 32) were for A 34.6, 17.5, and 26.3 grams, respectively, while for C they were 17.7 and 18.4 grams. Consequently, with A the amount of dextrose actually utilized after injection would be supplied in two experiments for about 2 hours by the amount absorbed, and in the other experiment for 4 hours, while for C the amount absorbed in both experiments would be sufficient for only $1\frac{3}{4}$ hours. If one considered only the increase in utilization of carbohydrate, then the amount supplied would suffice for a much longer period of time. The experiment of April 28, in which double the amount of dextrose was ingested (60 grams), shows the desirability of injecting more than 30 grams at one time. The percentage increase in the total metabolism supplied by carbohydrate has been calculated for April 28, taking as an actual increase 4 grams per hour, and has been found to be 27 per cent.

In this discussion two experiments have been omitted, because a 5 per cent alcohol solution was the medium in which the dextrose was given, and the course of the respiratory quotient indicates that there is no increase in carbohydrate utilization, or, if there were an increase, it was offset by the simultaneous metabolism of alcohol. Other experiments have been omitted because there was no marked difference between the average preliminary respiratory quotient and the maximum respiratory quotient. If, however,

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[1] Carpenter: Carnegie Inst. Wash. Pub. No. 303A, 1924, p. 104.

[2] Williams, Riche, and Lusk, loc. cit.; also, Carpenter, loc. cit., p. 104.

those experiments are included in which there was a positive difference between the minimum and maximum respiratory quotients, others might have been considered, as, for example, that of May 9, in which the quotients in the first hour after injection averaged materially lower than those in the second and third hours, showing that there was no apparent increase in the utilization of carbohydrate in the hour immediately following injection.

TABLE 34.—*Carbohydrate utilization before and after rectal injection of dextrose solutions.*

| Subject. | Date. | Before injection. | | | | After injection. | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Oxygen absorbed per minute.[a] | Average non-protein respiratory quotient. | Proportion of calories from carbohydrate. | Amount of carbohydrate as dextrose utilized per hour. | Oxygen absorbed per minute.[b] | Maximum non-protein respiratory quotient. | Proportion of calories from carbohydrate. | Amount of carbohydrate as dextrose utilized per hour. |
| | 1916. | *c. c.* | | *p. ct.* | *grams.* | *c. c.* | | *p. ct.* | *grams.* |
| A | Apr. 28 | 161 | 0.81 | 35.4 | 4.4 | 153 | 0.91 | 69.4 | 8.4 |
| | May 4 | 169 | .81 | 35.4 | 4.6 | 168 | .89 | 62.6 | 8.3 |
| C | May 11 | 234 | .85 | 49.0 | 8.9 | 233 | .87 | 55.8 | 10.2 |
| | 1917. | | | | | | | | |
| | Apr. 17 | 192 | .85 | 49.0 | 7.3 | 221 | .88 | 59.2 | 10.3 |
| A | Feb. 22 | 168 | .88 | 59.2 | 7.8 | 165 | .96 | 86.4 | 11.4 |

[a] Oxygen computed as used in katabolism of carbohydrate and fat.
[b] Oxygen used in katabolism of carbohydrate and fat as computed from the oxygen absorption for maximum respiratory quotient.

The experiments as a whole indicate very clearly that the effect of the injection of dextrose solutions by rectum is to increase the proportion of carbohydrate being utilized and consequently to increase the respiratory quotient. The amount actually absorbed in these experiments would hardly suffice for supplying the total carbohydrate utilization for more than 2 or 3 hours, except in one case when 60 grams were given. The effect of the dextrose solution upon the pulse-rate was not marked and was evident in but few of the experiments.

## UTILIZATION OF LEVULOSE WITH RECTAL INTRODUCTION.

The absorption studies of rectal injection of levulose showed positive results. As the amount obtained in the second wash-out was considerable and sometimes higher than that found in the first wash-out, it would seem that in many cases the unabsorbed material was not entirely removed. However, apparently the greater the quantity of material injected, the larger was the absorption. The absorption experiments consequently showed that the material ingested was available for utilization.

A study of the composition and volume of the urine indicates that the effect of levulose was somewhat different from that of the sodium-chloride solution, the alcohol, or the dextrose. In the first place, the changes in volume of urine eliminated as compared with the volume preceding injection were smaller percentagewise than with any of the other materials studied, and the liquid absorbed must have been retained rather than eliminated. Also the effect upon the nitrogen elimination was more positive with levulose than with most of the other substances, there being a decrease in the nitrogen elimination of 21 and 28 per cent in the two groups of levulose experiments.

This decrease can not be assigned to a smaller elimination of urine, as the volume excreted was either the same or slightly greater after injection as compared with that before. It would appear from this difference in effect upon the volume of urine that the liquid was withheld in order to retain the levulose, while on the other hand the decrease in the nitrogen elimination would point to a protective action on the part of the levulose.

In some of the levulose experiments there was a positive change in the pulse-rate in that it rose as a result of the injection. This is shown especially in the experiments with C on January 12, February 1, 7, and 15. However, there was not in every case a simultaneous increase in the respiratory quotient. This finding is of interest from the fact that it indicates that levulose has a stimulating action when introduced rectally without producing at the same time a metabolic change with consequent utilization of levulose. Of interest in this connection are similar results obtained by Joslin,[1] who found in several experiments that the levulose ingested orally produced no increase in the respiratory quotient and in some cases there was a fall. He also found[2] an increased oxygen absorption, a slight decrease in the respiratory quotient, and an increase in the heart-rate. His findings are similar to some extent to the results here in that there was an increase in heart-rate and some increase in oxygen absorption, with no marked change in the respiratory quotient.

The majority of the experiments show but little indication of increase in the carbohydrate utilization due to the rectal injection of levulose. In one experiment, however (that with subject A on January 18, 1916), there was a marked change in the respiratory quotient. In this experiment the subject received 50 grams of levulose in 500 c. c. of a sodium-chloride solution. The average respiratory quotient before injection was about 0.77, and $2\frac{1}{2}$ hours after injection there were three values which average about 0.93, or an increase of 0.16. This picture approximates more nearly the type of change in the respiratory quotient when levulose is given by mouth than that found in any other experiment. The subject reported in connection with the experiment that during the last hour he had cramps, but this was somewhat later than the period of the maximum respiratory quotient. In fact, from the other curves it would seem that the maximum respiratory quotient came before the change in heart-rate and in oxygen absorption. It is rather difficult to explain why in this particular experiment there was such a marked change in the respiratory quotient, which does not appear in any of the other 9 experiments. The non-protein respiratory quotient for the period before injection was about 0.76, and this, considering only the non-protein metabolism, would correspond to about 18 per cent of the katabolism coming from carbohydrate. The non-protein respiratory quotient at the period of the highest quotient was 0.95, which would correspond to 83 per cent of the non-protein metabolism coming from carbohydrate.

The fact that the majority of the experiments do not show so positive a rise in the respiratory quotients as one obtains when the substance is given by mouth would indicate that levulose was either retained unused or that its metabolism was of such a character that it did not result in a material change in the respiratory quotient, as, for example, would result when levulose is converted to glycogen. The general hypothesis as to the cause for the difference in metabolism between mouth feeding and rectal feeding follows.

[1] Joslin: Carnegie Inst. Wash. Pub. No. 323, 1923, p. 231.

[2] Ibid, pp. 302 and 309.

## HYPOTHETICAL DISCUSSION.

There are two explanations usually offered for the difference between the results obtained with rectal feeding and with oral ingestion. One is that the solutions introduced rectally are absorbed in the lower hemorrhoidal veins and that as these are not connected directly with the portal system, therefore the substances are introduced immediately into the general circulation and so distributed throughout the body. In this way the materials do not come to the liver at once in any quantity, but only indirectly. The other explanation is that the character of the results metabolically is due to the slow absorption of substances introduced rectally.

The lower hemorrhoidal veins are situated in a short section of the rectum and constitute but a very small portion of the venous circulation of the large intestine; the middle and upper hemorrhoidal veins join the tributaries to the portal circulation. Consequently, the idea that absorption would take place by the lower hemorrhoidal veins alone would be tenable only when the other portions of the venous circulation were closed off mechanically, or when the volume of the solution injected was so small that it could not reach the middle and upper portions of the colon. There have been some experiments in which a separation has been made, and in one of these glycosuria was produced, the only instance in which it has occurred with rectal feeding. The subjective impressions of our men would lead one to believe very strongly that the solutions generally passed well up into the transverse colon. Furthermore, Case has shown by X-ray that quantities of 1,000 c. c. or over always pass to the cecum. In fact, one of the much discussed questions in rectal injection is whether the ileocecal valve is "patent," i. e., open, and whether the material is absorbed because it gets beyond the cecum into the small intestine. In view of these facts it does not seem logical to accept the theory that substances injected rectally are absorbed solely in the lower hemorrhoidal veins.

Some observations in a recent study by Levy[1] on rectal introduction of digitalis have a bearing on the question as to how far solutions penetrate and from what part of the intestine absorption takes place. Levy administered rectally aqueous solutions of digitalis in volumes of 8 to 20 c. c., which were washed in with 25 c. c. of water. In a discussion of the anatomy of the large intestine, he comes to the conclusion that only a very small portion of the venous circulation connects directly with the systemic circulation, so that in order to agree with the general concept that the results of rectal feeding are due to direct entrance into the systemic circulation, one would have to believe that absorption took place in the lower part of the rectum only.

Levy conducted a series of tests to determine the depth to which solutions penetrated and the place where absorption took place. He injected by rectal tube 20 c. c. of a 15 per cent solution of sodium iodide, washed through with 25 c. c. of water. He then made roentgenograms of the abdomen 15 minutes, 2, 4, and 6 hours after injection. With three patients some of the solution was visible in the rectum immediately after it had been given, but most of it was in the lower sigmoid. With two of these cases some of the iodide could be seen as high up as the splenic flexure. With the fourth patient all of the iodide was in the sigmoid. With three cases it had disap-

[1] Levy: Arch. Intern. Med., 1924, 33, pp. 742–757.

peared in from 4 to 6 hours, and with the fourth a considerable amount was still present in the sigmoid and upper rectum 5 hours after injection. Iodide was also given in smaller quantities to two other patients, 15 c. c. of iodide solution being washed in with 15 c. c. of water. Again, although some was seen in the rectum, most of the solution passed into the distal loops of the sigmoid. Absorption was complete in 4 to 5 hours.

Levy comes to the conclusion that most of the digitalis given by rectum is taken into the venous circulation by the mesenteric and portal systems. He found that the effects of rectal digitalis therapy appeared at about the same time as similar doses by mouth, and concludes that the absorption rate of digitalis is about the same by rectal injection as by oral ingestion.

The idea that substances when rectally introduced are absorbed so slowly as to cause smaller changes in metabolism than when introduced by mouth has more ground for belief. Absorption is slow, particularly with reference to sugars, but the curves for the concentration of alcohol in urine show that the absorption must be nearly as rapid when the solution is injected rectally as when taken by mouth, so that difference in rate of absorption can not be the cause for difference in effect, particularly on the heart-rate. The greater effect upon the respiratory quotient when levulose is ingested by mouth can not be due solely to absorption, as the rise in the quotient is not proportional to the amount ingested. With 30 grams in a 500 c. c. solution given by mouth in this research, the rise in quotient was as prompt (see fig. 91, p. 159) as with 100 grams in a 300 c. c. solution in the experiments of Benedict and Carpenter.[1] In fact, the maximum increase (0.17) over the preliminary period with 30 grams was nearly as great as the maximum increase (0.23) in the 100-gram experiments. Accordingly, it is not solely the amount ingested which determines either the rapidity of the rise or the size of the increase in respiratory quotient.

Experiments are needed to determine the minimum quantity of levulose which will produce an increase in respiratory quotient. To insure like rates of absorption, the solutions in the mouth experiments should be given by the drop method, so as to have the conditions of ingestion similar to those in rectal feeding.

The difference in rate of absorption can not be the cause for a specifically different effect on metabolism when rectal injection takes place, for these experiments show that levulose, the sugar which was more readily absorbed, had less, if any, effect upon the respiratory quotient than did dextrose, the sugar less readily absorbed. In other words, with dextrose and levulose there is a reversed picture, so far as the respiratory quotient is concerned. Levulose produces the greater and more positive effect when ingested by mouth, and dextrose is the more effective in raising the respiratory quotient when rectally injected. The picture with the rectal injection of levulose and that with the rectal injection of dextrose thus differ specifically, and this difference can not be ascribed to differences in rate of absorption in rectal and oral feeding.

The idea that the effect of rectal feeding was due to slowness of absorption as compared with mouth feeding has been tested indirectly by other investigators. Lüthje[2] gave sugar by mouth in small portions at intervals through-

[1] Benedict and Carpenter: Carnegie Inst. Wash. Pub. No. 261, 1918, p. 242.
[2] Lüthje: Die Therapie der Gegenwart, 1913, p. 193. See p. 12.

out the day to diabetics who had shown complete urinary elimination of sugar when it was given by mouth and retention when it was given rectally. In these tests he found the same difference in utilization, and came to the conclusion that the differences were not due to slowness of absorption.

Bergmark[1] found different effects upon acidosis, according to whether dextrose was introduced by mouth or by rectum, but concluded that the slowness of absorption with rectal injection was not the cause, as he obtained a definite lowering of the acidosis within 2 hours when he gave six portions of 5 grams of dextrose each by mouth, at 30-minute intervals.

The experiments by Jahnson-Blohm[2] are of interest in this connection in showing that small quantities of dextrose (much smaller than the quantities actually absorbed rectally) increased definitely the blood-sugar. In three cases he gave 6.25 grams by mouth to a non-diabetic. In one of these experiments, the blood-sugar showed a definite rise in 15 minutes and in the other two in 30 minutes. Staub[3] found that 10 grams of dextrose in 100 c. c. of water produced an increase in the blood-sugar of 19 and 21 per cent over fasting values. These are mentioned in order to show that definite metabolic changes can be produced when small quantities of substances are introduced by mouth, and that in all probability the amounts and rate of absorption rectally are large enough to produce similar changes if the processes of metabolism are the same with rectal introduction as with oral ingestion.

A recent study by Gottschalk and Nonnenbruch[4] on the effect upon the urinary nitrogen and blood nitrogen of ingesting a mixture of amino-acids offers outside evidence on the differences in metabolism between oral and rectal ingestion. They used "rectamin," a commercial preparation of a mixture of amino-acids, designed for use in rectal feeding, and found that the ingestion by mouth resulted in an increase in the amino-acid nitrogen in the blood, but no increase in the proportion of amino-acid nitrogen in the urine. When, however, the material was given rectally, although a much smaller quantity was retained, the amino-acid nitrogen in the urine was increased markedly. They conclude that when the substance is absorbed rectally, part of it passes into the systemic circulation and avoids the liver. On reaching the kidneys it is eliminated. Gottschalk and Nonnenbruch believe that in passing through the liver the material is bound in some way to the serum substance, or that it is changed chemically in such a way that it is suitable for use by the various tissues, but that when such material does not pass through the liver, it is treated as foreign matter and is eliminated. This idea is in agreement with that of Varela and Rubino.[5]

From the evidence presented in this publication and that from other sources, it is clear that there is a specifically different metabolism when substances are injected rectally from that when they are introduced by mouth. The two explanations of the effect of rectal feeding, viz, avoidance of portal circulation and slowness of absorption, have been discussed in the preceding pages to show that some other conception is necessary to fit the results of our experiments. The following hypothesis is therefore offered:

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[1] Bergmark: Skand. Arch. f. Physiol., 1915, 32, p. 355.
[2] Jahnson-Blohm: Upsala Läkareförenings Förhandlingar, 1915, 20, p. 344.
[3] Staub: Zeitschr. f. klin. Med., 1921, 91, p. 44.
[4] Gottschalk and Nonnenbruch: Arch. f. exp. Pathol. u. Pharm., 1923, 99, pp. 300–314.
[5] Varela and Rubino: Med. Klinik, 1922, p. 831.

## Hypothesis Regarding the Metabolism with Rectal Feeding.

The material enters the rectum and colon and is absorbed both by the lower hemorrhoidal veins and by the upper and middle hemorrhoidal veins. From the two latter, the material enters into the circulation by way of the portal system and consequently passes through the liver. As the liver as well as the rest of the alimentary tract is in a quiescent state at the time that absorption takes place, there is no secretion of hormones or substances which are elaborated when material is ingested by mouth; consequently, the metabolism of the substance introduced rectally proceeds within the individual cells and tissues without the usual assistance and intercession of these hormones and secretions. This presupposes that a sufficient period of time has elapsed between the previous taking of food by mouth and the rectal injection, so that absorption, digestion, and all activity of the alimentary tract have ceased; otherwise, the material injected rectally would be utilized in the same way as when ingested by mouth with the liver and the alimentary tract in active operation. From this it should not be inferred that the chemical transformation necessarily takes place in the liver itself, but only that the transformation takes place *when the liver is in active condition.*

This hypothesis would imply that there are two distinct types of metabolism, one with the alimentary tract in a quiet state, that is, a metabolism which is universal throughout the body, and the other a metabolism with the alimentary tract in an active state which is superimposed upon the general metabolism throughout the body. Johansson[1] has also formulated the theory that there may be two independent metabolisms, namely, that there is a basal or ground metabolism which proceeds independently of any metabolism superimposed upon it, and that there is the metabolism of ingested material by means of which such material is either transformed or laid down in depots to form a reserve for the basal metabolism. In other words, his idea is that there is (1) a fundamental metabolism which proceeds exactly in the same manner, regardless of whether or not material is ingested, and (2) that there is a metabolism of ingested material which is superimposed upon the basal metabolism.

The hypothesis here presented would involve the idea that there may be two different types of metabolism, one the metabolism when the alimentary tract is in a quiescent state and the other the metabolism when digestion, absorption, transformation, and deposition are taking place. The former is similar to that during muscular work and the other that after a meal. It would appear that alcohol and dextrose are substances that can be utilized without the intervention of an active alimentary tract.

There is evidence that the liver forms a secretion after the ingestion of food or during its activity, also that the liver is in a more active condition after food ingestion. Cannon and Uridil[2] found that stimulation of the hepatic nerves caused an acceleration of the "denervated heart" when the adrenal glands had been removed, and that this acceleration was slight if the animal was fasting or in a poor condition and much greater when the animal was digesting meat.

Cannon and Griffith[3] sought further light on the nature of the substance

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[1] Johansson and Hellgren: Festschrift für Olof Hammarsten, 1906.
[2] Cannon and Uridil: Am. Journ. Physiol., 1921, 58, p. 353.
[3] Cannon and Griffith: Am. Journ. Physiol., 1922, 60, p. 544.

causing the acceleration. They found that the accelerator effect could be produced by reinjecting into the inferior vena cava some blood which had been drawn from the hepatic veins during stimulation. Feeding carbohydrate or fat was without influence, and the stimulation was most effective when milk or meat had been fed and the animal was digesting meat. They also injected intravenously amino-acids on the supposition that these might have been released by the liver during stimulation of the hepatic nerves, but tyrosine was the only one causing an increased heart-rate. Glucose, urea, catalase, or bile caused no acceleration of the heart-beat. They concluded that a substance of special and unknown nature is discharged into the blood-stream when the hepatic nerves are stimulated.

Asher[1] studied the perfused heart of the frog, using blood that had not passed through the liver, and subsequently perfused the same heart with blood which had passed through the liver of another frog. In the second case the heart-beats were augmented in size and in frequency. Similar experiments with tortoise heart gave results of like character. In both series the primary condition could be restored by perfusing with a fluid which had not passed through the liver.

Mann[2] has recently studied the activity of the liver and gall-bladder in the dog. He found that the liver during fasting sometimes secreted practically no bile, but that it was always much more active during digestion. He says he has come to regard the gall-bladder "as a part of a mechanism whereby the secretory activity of the liver is correlated with that of the gastro-intestinal tract", and further, "that the function of the gall-bladder is to stimulate the liver to increased activity at the time the gastro-intestinal tract is most active." He also states that he is coming to believe that the activity of the liver is associated with digestion.

These studies have been cited to show that there is evidence of and belief in the secretory activity of the liver, and that this activity is greater during digestion.

The hypothesis above outlined should be susceptible of experimental proof. If the increase in respiratory quotient due to the ingestion of levulose takes place when the alimentary tract is in active condition, then it ought to occur by whatever way it is introduced, provided the alimentary tract is active. For example, if protein is ingested by mouth and levulose by rectum, according to the hypothesis one would expect the respiratory quotient to rise. One would also expect the blood-sugar in the form of levulose to rise after the rectal injection of levulose, provided it is not immediately utilized. Rubino and Varela found slightly greater increase in blood-sugar with levulose than with dextrose after rectal injection. One condition should be conformed to in any study of the metabolism of rectal feeding, viz, that the time of making the experiment should be long enough after the last food in order to insure a quiescent state of the alimentary tract and accessory organs. This was not done in our experiments, and the variations in the results may be due to different conditions in the alimentary tract.

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[1] Asher: Proc. Soc. Exp. Biol. and Med., 1923–24, 21, p. 193.
[2] Mann: Journ. Am. Med. Assoc., 1924, 83, p. 829.

## SUMMARY.

The effect of rectal injection of solutions containing, respectively, 0.6 per cent of sodium chloride, 5, 7.5, and 10 per cent of ethyl alcohol, and varying amounts of dextrose and levulose was studied with four young medical students with special reference to absorption, the effect upon the flow and composition of urine, and the respiratory exchange.

The absorption of a 5 per cent alcohol solution was determined in 21 observations with 4 subjects. When the solution was injected rectally in quantities varying from 220 to 1,020 c. c. and with the time of retention over 2½ hours, the absorption was at least 98 per cent. The use of a second wash-out in 7 cases showed that the first wash-out removed practically all of the unabsorbed alcohol.

The absorption of 265 to 810 c. c. of a 7.5 per cent alcohol solution injected by rectum was determined in 6 cases with 3 subjects, and was found to be 98 per cent or over when the time of retention was somewhat over an hour. A second wash-out showed in all cases that the first removed all but extremely small quantities of alcohol.

The absorption of 260 to 265 c. c. of a 10 per cent alcohol solution was determined in 4 cases and found to be 99 per cent or over when the injection was retained for 2½ hours.

The absorption of 30 grams of dextrose in 500 c. c. of a 0.6 per cent sodium-chloride solution was determined in 8 cases and in 2 observations in which a 5 per cent alcohol solution was used as the medium. The amounts absorbed varied from 17.5 to 26.3 grams. The time of retention ranged from 2 hours and 17 minutes to 6 hours and 24 minutes. The amounts of dextrose recovered in the second wash-out varied from 0 to 3.5 grams. The absorption from 60 grams in 1,000 c. c. of a 0.6 per cent sodium-chloride solution was 34.6 grams in 5 hours and 25 minutes. The results as a whole indicate that the greater part of the absorption takes place in the first 2 hours, as lengthening the time of retention did not increase the absorption proportionately.

The absorption of 25 grams of levulose in 500 c. c. of a 0.6 per cent sodium-chloride solution was determined in 4 experiments, of 37.5 grams of levulose in 750 c. c. in one experiment, of 50 grams in 1,000 c. c. in 2 experiments, and of 50 grams in 500 c. c. in 3 experiments. From 16.2 to 21.8 grams were absorbed when 25 grams were injected and from 24.8 to 48.0 grams when 50 grams were given. The time of retention ranged in the whole series from 1 hour and 29 minutes to 4 hours and 35 minutes. In 4 cases the unabsorbed solution was voided naturally and the concentration of levulose was always found to be less than the concentration of the injected solution. This indicates that either unabsorbed material was diluted in the intestine or else that the levulose (solute) was absorbed more rapidly than the water (solvent). Sodium chloride was never found in the wash-outs.

The urine of the subjects was collected over a period of time beginning about an hour before injection and ending with the end of the observation. The concentration of alcohol in the urine was found to vary from 0 to 0.40 mg. per cubic centimeter when a 5 per cent alcohol solution was injected in the same quantities and with the same times of retention as in the absorption experiments previously mentioned. The proportion of the injected alcohol eliminated in the urine varied from 0 to 0.9 per cent. With a 7.5 per cent

alcohol solution injected in the same amounts and retained for the same periods as in the absorption experiments, the concentration of alcohol in the urine was 0 to 0.56 mg. per cubic centimeter, and the proportion eliminated from 0 to 1.2 per cent. Similarly, in the observations with a 10 per cent alcohol solution, the alcohol per cubic centimeter of urine varied from 0.10 to 0.33 mg. and the proportion eliminated from 0.4 to 0.7 per cent.

Six experiments were made in which 5, 7.5, and 10 per cent alcohol solutions were given by mouth in quantities containing 18.75 to 25 grams. The urine, collected in the same manner as in the rectal injection experiments, contained from 0.19 to 0.32 mg. per cubic centimeter and the elimination of alcohol given by this method was from 0.5 to 1.1 per cent.

There were 8 experiments with rectal injection of a 5 per cent alcohol solution in quantities equivalent to 420 to 750 c. c. in which the urines were collected in as short periods as possible (approximately 30 minutes to 1 hour) over a period of $3\frac{1}{2}$ to $6\frac{1}{2}$ hours, also one experiment with rectal injection of 250 c. c. of a 10 per cent alcohol solution under like conditions. The maximum concentration was 0.35 mg. per cubic centimeter with the 5 per cent solution and 0.36 mg. per cubic centimeter with the 10 per cent solution. The peak of concentration occurred within 2 hours from the beginning of the injection. When the amount injected was 500 c. c. of a 5 per cent solution or under, alcohol was not present in the urine at the end of 5 hours.

Three experiments of similar character, with 500 c. c. of a 5 per cent solution, and one with 250 c. c. of a 10 per cent solution, all taken orally, gave as a maximum concentration 0.38 mg. per cubic centimeter, the peak occurring within the first 2 hours. In only one experiment with a 5 per cent solution was the collection continued until there was no alcohol in the urine, viz, 5 hours.

There were four urines which gave evidence of the presence of conjugated alcohol.

The rectal injection of alcohol solutions caused an average increase in the volume of urine ranging from 47 to 193 per cent, comparing the urine collected during the experimental period with that before the experiment. (See table 20, p. 73.) The nitrogen elimination decreased 5 to 19 per cent, and the sodium-chloride elimination decreased 25 to 81 per cent.

The rectal injection of a 0.6 per cent sodium-chloride solution increased the volume of urine on the average 52 per cent, increased the nitrogen elimination 2 per cent, and decreased the sodium-chloride output 32 per cent.

The rectal injection of 30 grams of dextrose in 500 c. c. of a 0.6 per cent sodium-chloride solution in 7 experiments and in 500 c. c. of a 5 per cent alcohol solution in 2 experiments caused an average increase of 73 per cent in the volume of urine, an average decrease of 13 per cent in the nitrogen elimination, and an average decrease of 9 per cent in the sodium-chloride elimination.

The rectal injection of 25 grams of levulose in 500 c. c. of a 0.6 per cent sodium-chloride solution resulted in an average increase of 7 per cent in the urinary volume, an average decrease of 21 per cent in the nitrogen elimination, and an average decrease of 58 per cent in the sodium-chloride excretion. The rectal injection of 37.5 to 50 grams of levulose in 500 to 1,000 c. c. of a 0.6 per cent solution of sodium chloride caused an average increase of 15 per cent in the volume of urine, an average decrease of 28 per cent in the nitrogen

elimination, and an average decrease of 67 per cent in the sodium-chloride output.

The measurement of the respiratory exchange by means of the collection and analysis of expired air and the count of the heart-rate were made before and after rectal injection of a 0.6 per cent sodium-chloride solution in 14 experiments with 3 subjects. The average heart-rate was 6 beats per minute lower, the average oxygen absorption per minute 20 c. c. lower, and the average respiratory quotient unchanged at the end of 3 hours after injection began, as compared with the 40-minute period before injection.

Four experiments of a similar character were made with one of the subjects in which the respiratory exchange was measured by means of a chamber apparatus connected with a closed circuit. The pulse-rate remained practically unchanged, the carbon dioxide and respiratory quotient rose slightly over a period of 6 hours after injection, while the oxygen absorption rose less, or not at all.

The respiratory exchange and heart-rate were measured in 16 experiments with 3 subjects before and after the rectal injection of 220 to 1,020 c. c. of a 5 per cent alcohol solution. The average heart-rate showed an increase of 5 beats per minute at the end of 2½ hours, as compared with the minimum average before injection. The average oxygen consumption per minute gave a maximum increase of 8 c. c. per minute (3.5 per cent) at the end of 1½ hours, which did not disappear at the end of 4 hours after rectal injection began. The average respiratory quotient fell 0.02 by the end of 1 hour and remained lowered at least 3 hours.

The respiratory exchange and pulse-rate were measured with 3 subjects in 8 experiments in which the collection of expired air was made, and its composition determined before and after the rectal injection of 265 to 810 c. c. of a 7.5 per cent alcohol solution, also in 5 experiments with one subject in which the respiratory exchange was determined by means of a chamber and closed circuit respiration apparatus before and after the rectal injection of 500 c. c. of a 7.5 per cent alcohol solution. In the first group there was a rise in the pulse-rate from an average of 67 beats immediately after injection to 71 beats 1½ hours after injection, a rise in the average oxygen absorption of 18 c. c. (7.5 per cent) within 1½ hours after injection, and a gradual lowering of the average respiratory quotient from 0.84 before injection to 0.76 at the end of 4 hours after injection. In the group with the chamber apparatus, the average pulse-rate rose steadily from an average of 62 beats in the hour before injection to 73 beats at the end of 6½ hours after injection, the average oxygen absorption increased from 186 to 225 c. c. in the same period, and the respiratory quotient fell from 0.84 to 0.77. There was no indication of a return to normal during this time.

Four experiments with rectal injection of 265 c. c. of a 10 per cent alcohol solution showed changes of the same character as with the 5 and 7.5 per cent alcohol solutions, but not to so marked a degree.

In 6 alcohol experiments the pulse-rate and respiratory exchange were determined after ingestion by mouth; in 3 experiments after 400 c. c. of a 5 per cent solution, in 2 experiments after 250 c. c. of a 7.5 per cent solution, and in 1 experiment after 250 c. c. of a 10 per cent solution. Immediately after the ingestion there was a rise of 3 beats per minute in the average pulse-rate, with a fall of 5 beats at the end of 2 hours, followed by a subsequent rise of 9

beats per minute. Oxygen absorption decreased by 10 c. c. is shown for $2\frac{1}{2}$ hours after ingestion, with a return at the end of 4 hours to slightly above the preliminary value. There was an immediate fall in the average respiratory quotient which amounted to 0.05 in 1 hour, and the quotient did not return to normal in 4 hours.

The respiratory exchange was measured by the collection and analysis of expired air before and after rectal injection of 30 grams of dextrose in 500 c. c. of a 0.6 per cent sodium-chloride solution in 5 experiments, in 500 c. c. of a 5 per cent alcohol solution in 2 experiments, and in 1 experiment after rectal injection of 60 grams of dextrose in 1,000 c. c. of a 0.6 per cent sodium-chloride solution. The chamber and closed circuit method was used in 2 experiments, with injection of water or sodium-chloride solution. The pulse-rate, which was counted in all of the experiments, showed a rise beginning $1\frac{1}{2}$ to 2 hours after injection which amounted to about 5 beats at the end of 4 hours. The average oxygen absorption was influenced but little. The average respiratory quotient rose from a minimum of 0.81 before injection to over 0.86 about $2\frac{1}{2}$ hours after injection.

The respiratory exchange was measured by the collection and analysis of expired air and the pulse-rate counted in 10 experiments with 3 subjects after the rectal injection of 25 to 50 grams of levulose in 500 to 1,000 c. c. of a 0.6 per cent sodium-chloride solution. The pulse-rate rose slightly in the first $1\frac{1}{2}$ hours after injection, with a slight fall during the next $2\frac{1}{2}$ hours. The average oxygen absorption was very slightly increased within an hour after injection. The respiratory quotient showed an increase of 0.03 at the end of $2\frac{1}{2}$ hours, compared with the average at the beginning of injection.

Suggestions are given as to lines of investigation needed to elaborate and supplement the data already accumulated.

A theoretical discussion of the utilization of alcohol is given as calculated from the changes in the concentration of alcohol in the urine and the changes in the respiratory quotient, with the conclusion that 25 grams will be utilized in 5 hours. The calculation of the maximum theoretical increase in the utilization of dextrose is made from the change in the respiratory quotient. A theoretical discussion of the utilization of levulose when introduced rectally is likewise given.

The differences between mouth and rectal feeding are considered both with reference to the experiments here reported and to the observations of other investigators. The hypothesis is proposed that substances injected rectally are absorbed both by the rectal venous circulation (systemic) and by the colonic venous circulation (tributaries of the portal system), distributed throughout the body, and metabolized without the aid or the intervention of secretions or hormones elaborated when the material is ingested by mouth. This hypothesis assumes, however, that the rectal injection is carried out long enough after the ingestion of food by mouth so that the alimentary tract and accessory organs are at rest.